Fatal pulmonary fibrosis: a post-COVID-19 autopsy case

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ABSTRACT

There is growing evidence of histopathological changes in autoptic individuals infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2); however, data on histopathological changes in autopsied patients with eradicated COVID-19 are limited. We performed an autopsy on a Caucasian female in her 80s, who died due to severe, bilateral pulmonary fibrosis after eliminated SARS-CoV-2 infection. In addition, CT scans from 2 months before infection and from 6 days prior to death were compared. Comparison of the CT scans showed bilateral development of widespread fibrosis in previously healthy lungs. Microscopic examination showed different areas with acute and organising diffuse alveolar damage and fibrosis with honeycomb-like remodelling and bronchial metaplasia. We here report a unique autopsy case with development of widespread pulmonary fibrosis in a woman in her 80s with previous COVID-19 and no history of pulmonary illnesses.

BACKGROUND

In late 2019, the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) emerged in Wuhan, China. As of 12 July 2020, there are over 12 million confirmed cases and more than 550 thousand confirmed deaths of COVID-19 worldwide.1 The relatively few autopsy studies performed on patients with COVID-19 so far reveal acute histopathological changes such as diffuse alveolar damage (DAD) with hyaline membranes, squamous bronchial metaplasia, myocarditis and widespread microvascular thromboembolisms.2–11 The long-term effects of COVID-19 are, however, not fully elucidated, but speculations are being made if pulmonary fibrosis could be a consequence of the infection.12 Acute respiratory distress syndrome (ARDS), reported in as many as 42% of hospitalised patients with COVID-19 in Wuhan, China, is a known cause of pulmonary fibrosis.13 There is an increasing focus on sequelae in patients post COVID-19, and pulmonary fibrosis has been demonstrated on CT scans in COVID-19 survivors.14 Histopathological findings of pulmonary fibrosis include dense fibrosis with patchy and perilobular involvement, honeycomb remodelling and fibroblastic foci.15

To our knowledge, no autopsy cases on patients with previous COVID-19 existed at the time of submission of this manuscript. This case report aimed to report the histopathological findings in a woman in her 80s with eradicated COVID-19.

CASE PRESENTATION

The patient was a woman in her 80s with a history of well-treated atherosclerosis, a previous transitory cerebral ischaemia in 2013, stable angina pectoris with normal echocardiography in 2016 and 2018, and breast cancer (lumpectomy and adjuvant radiation therapy in December 2019) with no metastatic spread. The lungs were not irradiated during the radiation therapy. Prior to hospitalisation, she received acetylsalicylic acid and a statin daily in addition to regular vaginal oestradiol, and irregular sublingual nitroglycerine for stable angina pectoris. The patient was a never smoker with no history of pulmonary illnesses, had no history of excessive alcohol use, was self-sufficient in her daily life and physically active with daily walks and a good performance status. A CT scan was performed to monitor the patient’s recovery from breast cancer on 31 January 2020, which showed normal conditions of the lungs (see figure 1A,B).

On 31 March 2020 (day 1), the patient was admitted to hospital due to exacerbation of breathing difficulties and chest pain. Prior to this episode, she had had a week of flu-like symptoms with fever. The patient was shortly after arrival to hospital intubated and transferred to the intensive care unit. COVID-19 was confirmed with reverse transcriptase PCR (RT-PCR) of endotracheal aspirate. She developed severe ARDS and was initially treated according to guidelines including lung-protective ventilation (tidal volume 6 mL/kg predicted body weight, high positive end-expiratory pressure, driving pressure <15 cm H2O, plateau pressure <30 cm H2O), heavy sedation/neuromuscular blockade, prone positioning and inhaled nitric oxide. On day 18 of hospitalisation, uncomplicated tracheostomy was established and, subsequently, assisted spontaneous breathing. A CT scan revealed large bilateral central pulmonary embolisms without haemodynamic influences that were treated with high-dose dalteparin. She tested positive for COVID-19 in endotracheal aspirates on days 1, 2, 7, 14, 21 and 23, and tested negative on days 36 and 44 and was, subsequently, unisolated. Despite extensive examinations including multiple bronchoscopies, the patient did not test positive for any other microbiological pathogen. A high-resolution CT scan from day 39 showed bilateral consolidations, septal thickening, traction bronchiectasis and infiltrative and parenchymal changes corresponding with widespread pulmonary fibrosis (see figure 1C–F).
The heart was enlarged and weighed 380 g. The right ventricle had a normal thickness (3 mm), whereas the left ventricle was concentrically hyperplastic (23 mm). Tissue samples were selected from the heart, spleen, liver, kidneys, pancreas, a retroperitoneal lymph node, lymph nodes from the lung hilum on both sides, columnar bone marrow and the root of mesentery.

In order to fully inflate the collapsed lung compartments and better visualise histopathological changes, perfusion fixation of the removed lung block was performed. Perfusion fixation was performed by injection of a buffered 10% formalin solution with a 50 mL syringe in various sections of the lungs. A total of 550 mL was injected in the right lung and 650 mL in the left lung. After fixation, the lungs were cut, and on the cut surfaces of the lungs widespread fibrosis was found and was most prominent in the apical lung lobes (see online supplementary material). Multiple tissue samples were selected from all lobes including the fibrotic changes visible on gross examination. Representative sections of tissues from both the autopsy and from the perfusion fixated lungs were formalin fixed in cassettes, paraffin embedded, sliced, stained with H&E and, subsequently, examined in a light microscope.

All lung samples showed severe reactive and inflammatory changes. The architecture was destroyed in larger areas with fibrous organisation and collagenised fibrosis (see figure 2).

Widespread angiogenesis was seen as well as focal bleeding. Local moderate chronic inflammation was present and dominated by lymphocytes. Honeycomb-like fibrosis with enlarged airspaces with bronchial metaplasia was present in some areas. In areas with more preserved lung architecture, the pneumocytes had a reactive appearance. A small subpleural area showed alveoli with hyaline membranes representing the acute stage of lung injury, as is seen in acute DAD. In total, the changes represent different stages of lung injury with acute to organising DAD and fibrosis with a honeycomb-like pattern and bronchial...

Figure 1  CT images of severe, bilateral pulmonary fibrosis following COVID-19. (A and B) Apical and basal axial views from a CT scan on 31 January 2020 (2 months prior to COVID-19), showing normal lung fields. (C and D) Corresponding axial views from 8 May 2020, showing consolidations, septal thickening, traction bronchiectasis and infiltrative and parenchymal changes consistent with pulmonary fibrosis. (E and F) Coronal posterior midline and midline views from the same high-resolution CT scan.

Ultimately, the patient herself in collaboration with the treating physicians and her relatives decided to stop active treatment. Treatment was terminated on day 45 and she passed away a few hours after. The family gave consent for a medical autopsy to be performed without neuropathological examination, which was, subsequently, performed 4 days postmortem.

INVESTIGATIONS

The autopsy was performed according to protocol at Aarhus University Hospital corresponding to national guidelines from the Danish Pathology Society. It was performed in a ventilated room and the pathologist, resident pathologist and the technician wore protective disposable gowns, disposable scrub caps, FFP2 masks with face shields, gloves and rubber boots. The organs were eviscerated in toto. Lungs, trachea, larynx and thoracic aorta were not dissected during the autopsy but were left together for later perfusion fixation. On gross examination of the internal organs, the lung surfaces showed signs of widespread pulmonary fibrosis with a bosselated ‘cobblestone’ appearance (see online supplementary material). An occluding residue of the previous fibrosis with a bosselated ‘cobblestone’ appearance (see online supplementary material).

Figure 2  Histopathological findings demonstrating different stages of lung injury. (A) Acute diffuse alveolar damage (DAD) in the right upper lobe with hyaline membrane formation (→) (H&E ×100). (B) Organising DAD in the lower left lobe with haemorrhage, fibrin deposits (↑) and beginning organisation of immature fibroblasts (←) (H&E ×100). (C) Organisation of immature fibroblasts in the left upper lobe (↑). (D) Fibrosis with honeycomb-like remodelling in the right upper lobe (←) (H&E ×20) with bronchial metaplasia (↑) and marked chronic inflammation with primarily lymphocytes (H&E ×100).
metaplasia. The rest of the tissue samples showed postmortem autolysis and congestion with no other significant abnormalities. Specifically, the tissue samples from the heart were normal and there was no evidence of microthrombosis in any of the tissues.

DISCUSSION

This is, to our knowledge, the first autopsy case report of a patient with previous COVID-19. The patient had no history of pulmonary illnesses prior to infection and had a normal CT scan of the lungs with no evidence of pulmonary fibrosis just 2 months before COVID-19. During histopathological examination, we found, in addition to changes commonly found in DAD, fibrotic areas with honeycomb-like remodelling and bronchial metaplasia; changes commonly observed in interstitial lung diseases such as usual interstitial pneumonia.

Mechanical ventilation is known to potentially cause ventilator-induced lung injury (VILI), though, the risk is greatly minimised with the previously described treatment guidelines of ARDS that the patient was treated under. The pathology seen in VILI is similar to that seen in ARDS. The contributing role of mechanical ventilation in the histopathological findings is, therefore, difficult to distinguish from that of COVID-19.

As of yet, the long-term sequelae of COVID-19 are unknown. Follow-up studies are needed to determine the potential pulmonary fibrosis and its extent in COVID-19 survivors. In addition, there is a substantial need for autopsies of patients with ongoing and terminated COVID-19 to determine the acute and chronic histopathological changes of the disease. If pulmonary fibrosis is a long-term complication in patients with severe COVID-19, there is an unfortunate possibility of a second wave of COVID-19 related sequelae and deaths. Also, early recognition and acknowledgement of pulmonary fibrosis in COVID-19 survivors fuel the possibility of initiating potential antifibrotic treatment to prevent further progression of pulmonary fibrosis.

The authors do not propose that the widespread pulmonary changes reported here are representative of all patients with COVID-19, but the morbidity and mortality of pulmonary fibrosis following COVID-19 should be taken into consideration by physicians when treating patients with COVID-19 and the healthcare system in general when managing COVID-19 survivors with complications.

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REFERENCES