Histopathological Features of the Lung Parenchyma in a 64-Year-Old Male Patient with Post-COVID-19 Infection with Spontaneous Pneumothorax Dextra Due to Alveolar-Pleural Fistula (APF): A Case Report

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ABSTRACT
Introduction: Histopathological features of the lung parenchyma due to the Alveolar-Pleural Fistula (APF) in a patient with post-COVID-19 infection have not been reported. APF usually occurs after a spontaneous pneumothorax. Spontaneous pneumothorax is an abnormal traumatic accumulation of air within the pleural space. It is classified as primary or secondary pneumothorax based on multiple risk factors.

Case Presentation: A sixty-four-year-old patient was referred from one of the remote hospitals in the west of Bali due to spontaneous simple pneumothorax dextra. A week after being diagnosed with COVID-19 infection, the patient underwent a bullectomy procedure and was clinically diagnosed with recurrent spontaneous pneumothorax dextra due to APF. Then, the bullectomy specimen was sent to the anatomical pathology laboratory. Histopathology test revealed extensive areas of necrosis and fibrosis with scattered lymphocytes and emphysematous alveoli found in APF lesions.

Conclusions: In conclusion, the evidence of extended fibrosis, which destroys the pulmonary parenchymal septum and dilated alveoli with diffuse fibrosis in the subpleural and intraparenchymal areas, may cause impairment of both perfusion and ventilation. Unfortunately, viral cytopathic like-changes related to COVID-19, such as multinucleated cells with large nuclei, amphiphilic cytoplasm, and prominent nucleoli in alveolar spaces with intranuclear inclusions, were not found in this case. In this case, surgery is needed in case of fistula, either related or unrelated to infection of the pleural cavity indicating the patient’s functional recovery.

INTRODUCTION
Histopathological features due to the Alveolar-Pleural Fistula (APF) of lung parenchyma in a patient with post-COVID-19 infection have not been reported. APF is a persistent air leak that becomes the major cause of persistent pneumothorax. It is indicated by prolonged air bubbling into the chest drainage system. Mostly, the air leak is caused by a post-operative procedure like transbronchial lung biopsies and ultrasound-guided thoracentesis, with incidence rates between 0–6% and 2.7–3.6%, respectively [1]. Apart from being associated with spontaneous pneumothorax, it is infrequently for some APF cases to be associated with pulmonary infections like pneumonia, malignancies such as pulmonary metastasis, barotrauma due to mechanical ventilation, chest trauma, and iatrogenic etiologies that can occur after thoracentesis or chest tube insertion [2,3]. Spontaneous pneumothorax is also an abnormal traumatic accumulation of air within the pleural space. It is classified as primary or secondary pneumothorax, correlated with multiple risk factors [4]. Here, the writers present a case of APF due to spontaneous pneumothorax caused by multiple pulmonary bullae bilateral following COVID-19 infection, focusing on histopathological findings of lung parenchyma.
CASE PRESENTATION

A sixty-four-year-old patient was referred from one of the remote hospitals in the west of Bali due to spontaneous simple pneumothorax dextra. In the emergency room, the patient looked very ill and suffered from shortness of breath, which was getting worse on the last day before hospital admission. His vital sign at the emergency room showed blood pressure of 100/80 mmHg, slightly increased temperature of 37.8 °C, respiratory rate of 28–30 times/minute, and peripheral oxygen saturation of 90%. Not knowing his medical history, the patient said he only had smoking habits for more than ten years. His swab test on September 27 revealed a positive result for novel coronavirus disease 2019 (COVID-19). His complete blood count was neutrophils 51.88% (47–80), lymphocyte 29.82% (13–40%), monocyte 4.43% (2.0–11.0), hemoglobin 13.02 (13.5–17.5 g/dl), and platelet 303.4 (150–440 103/µL). In addition, thorax CT-scan results revealed fluid-pneumothorax dextra and bilateral apex pulmonary bullae (Figure 1).

A week after hospitalization, the patient underwent a bullectomy procedure with a clinical diagnosis of recurrent spontaneous pneumothorax dextra due to APF. Then, the specimen was sent for pathology examination (Figure 2). The entire tissue was processed through a routine histopathologic method.

The microscopic examination revealed fibrotic lung parenchymal with reactive and proliferative myofibroblast. The fibrotic area diffusely appeared subpleural and patchy in the intraparenchymal and interalveolar areas (Figure 3). Half of the lung alveoli were also distended

Figure 1. MS CT Scan thorax. (A), (B) Multiple pulmonary bullae at the lung apex bilateral (star); (C) Fluidopneumothorax dextra (head arrow).

Figure 2. Macroscopic. Tissue pieces with an overall size 5x2x0.5 cm, irregular shaped, spongy, and some tissue on their surface have a reddish spot. On the wedge of the tissues, there was a black area.

Figure 3. Microscopic findings of bullectomy specimen. (A), (B) Histologic feature of emphysema. Section lung tissues show fragmented, destructive septum and some dilated alveoli with a diffuse fibrotic area at the subpleural and intraparenchymal area (inset); (C), (D) Destruction of parenchyma (normal alveoli are replaced by spaces lined by cuboidal epithelium, head arrow), septum interalveolar fibrosis with scattered lymphocyte infiltrate (star).
with the destructive septum (emphysematous). At the alveoli spaces, there was a huge amount of macrophages, and some of them contained pale amorphous eosinophilic substances. On the other focus, there was also lymphocyte infiltrate and carbon debris deposits. In addition, dilated blood vessels containing neutrophils and areas of necrosis were also found. Based on the above findings, histomorphology features of the lung parenchymal bullectomy tissue showing extensive fibrosis with lymphocytic inflammatory cells and areas of necrosis and an emphysematous alveolar feature can be found in the APF lesion.

DISCUSSION

The patient, in this case, suffered from shortness of breath due to persistent air leak in an alveolar-pleural fistula, causing a gap for air communication between the pulmonary parenchymal, distal the segmental bronchus, and the pleural cavity. The common causes include ruptured bulla, cavitary neoplasm, radiation-induced pulmonary interstitial fibrosis, necrotizing pneumonia, and post-thoracic surgical intervention. The writers focus on histopathology findings based on bullectomy specimens showing chronic lung parenchymal changes. Chronic changes due to chronic inflammation of lung parenchymal can arise in the following settings: persistent infection, hypersensitivity disease, prolonged exposure, and potentially toxic agents, either exogenous or endogenous.

The persistent infection is caused by a microorganism that is difficult to eradicate, such as mycobacteria, certain viruses, fungi, and parasites [4]. These organisms often evoke an immune reaction called delayed-type hypersensitivity. However, any specific chronic inflammatory changes, such as granulomatous lesions often associated with mycobacterium tuberculosis infection or sarcoidosis, were not found in this case. Likewise, the features of the COVID-19 virus in the form of viral cytopathic effects, such as multinucleated cells with large nuclei, amphophilic cytoplasm with prominent nucleoli, and intranuclear inclusions, were also unfortunately not found in the microscopic feature of this case [5-6]. Moreover, it should be noted that unresolved acute inflammation can also evolve into chronic inflammation, and morphologically, chronic inflammation is characterized by the infiltration of mononuclear inflammatory cells, such as lymphocytes, macrophages, and plasma cells. Tissue destruction can also be caused by persistent infectious agents or inflammatory cells and is characterized by the formation of connective tissue that replaces damaged tissue, which is microscopically illustrated by the angiogenesis and fibrosis processes [4]. Some literature states that the binding of coronavirus to angiotensin-converting enzyme 2 (ACE2) receptors and angiotensin II can directly damage pneumocytes by activating the immune cell system, which reduces the production of surfactant and lung elasticity and plays a role in the development of fibrosis [7]. Although fibrotic changes caused by infection of COVID-19 were not significant, fibrotic changes were found in 22% of the cases. However, pulmonary changes are the most significant things, although nonspecific [8,10].

The other report uncovered diffuse alveolar damage (DAD) and divided it into three phases. The first is the exudative phase, in which the morphological changes are characterized by the formation of hyaline membranes, desquamation of pneumocytes, cellular or proteaceous exudates, and alveolar hemorrhage and fibrinoid necrosis of small vessels. Second, the organizing phase is marked by fibroblasts’ interstitial and intra-alveolar proliferation, lymphocytic infiltration, type II pneumocyte hyperplasia, and fibrin deposition. Meanwhile, the fibrotic phase is indicated by dense collagenous fibrosis and architectural remodeling. On the other hand, the pattern of lung injury is also classified into three phases: 85% are characterized by epithelial changes, such as diffuse alveolar damage with varying degrees of organization, denudation, and pneumocyte hyperplasia; 59% show vascular changes, such as diffuse intra-alveolar fibrosis, microvascular damage, microthrombi, acute fibrinous, and organizing pneumonia; 22% indicate fibrotic changes consisting of fibrotic diffuse alveolar damage or interstitial fibrosis [9-10]. In this case, subpleural and intraparenchymal fibrosis may be part of the fibrotic phase of lung injury, and smoking history may exacerbate pulmonary emphysema. Unfortunately, in this case, the microscopic changes associated with COVID-19 virus infection were not found, i.e., changes in the cytopathic effect of the virus, such as multinucleated cells with large nuclei, amphophilic cytoplasm, and prominent nucleoli with intranuclear inclusions in the alveolar clefts.

Later, the patient was discharged from the hospital a week after the bullectomy, and he said he could do light exercise and normal daily living activities with a little help from his daughter. He also had a pulmonary function test shortly before being discharged from the hospital, and the results showed the percentage of vital strength capacity (65-68%), which was classified as moderate for restrictive lung function. The patient was then suggested doing chest physiotherapy to improve his lung performance.

CONCLUSIONS

The evidence of extended fibrosis, which destroys the pulmonary parenchymal septum and dilated alveoli with diffuse fibrosis in the subpleural and intraparenchymal areas, may cause impairment of both perfusion and ventilation. Based on British Thoracic Society guidelines, a surgical opinion should be indicated
in cases of medical intervention for persistent air leak fail and failure of the lung to re-expand after 3–5 days. In this case, surgery is needed in the case of fistula, either related or unrelated to infection of the pleural cavity indicating the patient’s functional recovery.

DECLARATIONS

Competing of Interest
The authors declare no competing interest in this study.

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REFERENCES