The Review of Histopathological Pulmonary Findings of COVID-19: What We Learned from Postmortem Biopsy and Autopsies; Beyond the Horizon

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Dear Editor,

A pneumonia outbreak began in China in December 2019, and a new coronavirus was identified as the causative agent. The disease was called coronavirus disease 2019 (COVID-19) [1]. Nearly 20%-30% of the patients with the COVID-19 infection require hospitalization. This disease may progress to acute respiratory distress syndrome, which is characterized by refractory hypoxia, bilateral infiltration in the chest, high mortality [2] sepsis, multiple organ failure, and death [3]. Taking potential complications into account, we do not have sufficient histopathological data because it is not possible to perform biopsy on all the patients; however, there are recently published pulmonary pathology results of postmortem biopsies and autopsies.

In a study by Lacy et al. the autopsies of deaths related to COVID-19 showed that the lungs were moderately heavy, edematous, and relatively stiff. There were areas of hemorrhage in the right upper, middle, and left lower lobes of the lung. Histopathological examination revealed focal/extensive hyaline membranes, intra-alveolar macrophages and reactive pneumocytes, discrete pneumocyte hyperplasia, irregular mononuclear infiltrates, and multinuclear cells along the alveolar septa. They reported that no specific cytopathic effects on fibroblast proliferation focus, granuloma, or foreign body were observed. Pulmonary pathology was in the form of early diffuse alveolar damage (DAD) and was found to be similar to that seen in severe acute respiratory syndrome (SARS) autopsies [4].

Similarly, according to an article published recently, histopathological characteristics of the early phase of COVID-19 infection were revealed in 2 patients who underwent surgical resection for adenocarcinoma, and these patients were found to have COVID-19 infection at the time of surgery. The findings were not specific in these cases. Although hyaline membranes were not observed, pneumocyte hyperplasia, focal inflammation, multinuclear giant cells, and hyperplastic pneumocytes suspected of being viral inclusions in some cases were seen. Considering that these patients were asymptomatic for COVID-19 during the surgery, it is more likely that they reflect only early changes of acute lung injury in infection. In the 2 patients presented in the study, acute lung injury was found in the proliferative and exudative phases. Other changes of chronic process, such as organization and squamous metaplasia, were not found [5].

The results of postmortem biopsies performed by Coppin et al. on 6 patients who were COVID-19-positive and at different stages of the disease were published. In the postmortem examination of the first patient who died early in the course of the disease, 5 days after the onset of fever, they found a lymphocytic viral pneumonia, infiltration of the alveolar walls by numerous lymphocytes and edema, and type 2 pneumocyte hyperplasia with cytologic atypia. In 5 other patients who died nearly 20 days after the beginning of the symptoms, they found that the histological pattern was an acute, fibrinous, and organizing pneumonia (AFOP) characterized by an extensive intra-alveolar fibrin deposition called fibrin balls rather than hyaline membranes. AFOP is a cortico-sensitive pathology, especially in its subacute presentation, with fibrin present in both alveolar spaces and bronchioles as well as endothelial injury in contrast to the fulminant pre-

sentation. As a result, the damage in the lungs was not found to be DAD in SARS-coronavirus 2 infection [6].

Zhang et al. published the pulmonary findings of a 72-year-old male patient with a history of diabetes and hypertension who presented with fever and cough. On postmortem transthoracic needle biopsies, they described histopathologic changes in the lung of the patient who died 3 weeks after diagnosis despite antiviral therapies. They reported that the histomorphological findings were consistent with those of DAD and in pattern of organizing pneumonia reflecting the chronic process. Histopathological examination revealed DAD organizing phase, and they noted that desquamate alveolar cells, chronic inflammatory infiltrates, alveolar fibrinous exudates, and reactive type II pneumocyte hyperplasia were present. They also noted intra-alveolar loose fibrous plugs within the small airspaces (organizing pneumonia). Immunostaining performed using rabbit polyclonal antibodies against Recombinant protein3 nucleocapsid protein (Rp3 NP) protein demonstrated prominent expression on the alveolar epithelial cells, including damaged and desquamated cells within the alveolar space [7].

Fox et al. published the results of 4 autopsies in a series of patients. Macroscopic examination revealed that the lungs were heavier than usual, were erythematous, and had hemorrhagic areas. In the histopathological examination, it was found that all the patients demonstrated bilateral DAD with hyaline membranes and hemorrhage, and fibrin thrombi were present within the distended small vessels and capillaries. They noted that the examination revealed comparatively mild-to-moderate lymphocytic infiltrate, located predominantly in the interstitial spaces and around larger bronchioles. CD4+ lymphocytes could be seen in aggregates around the small vessels. In all the patients excluding 1, hemorrhage foci were present. Desquamated type 2 pneumocytes with apparent viral cytopathic effect, including eosinophilic nucleoli, were present within the alveolar spaces. They also noted that it consisted of viral inclusions, likely representing viral cytopathic effect. The alveolar capillaries were notably thickened with surrounding edema, and fibrin thrombi were present. A notable finding was the presence of numerous megakaryocytes with nuclear hyperchromasia and atypia within the small vessels and alveolar capillaries, highlighted by CD61 and von Willebrand factor immunostains. In this initial series of autopsies including thrombotic microangiopathy ,these cells were located within the alveolar capillaries and associated with actively producing platelets [8].

The mentioned series of patients show that COVID-19 is likely to cause various different patterns in the lungs, such as DAD, lymphocytic pneumonia, and AFOP. Presence of these patterns is associated with the duration of the disease. DAD-dominant pattern was observed in all patients with disease duration of less than 10 days, and AFOP-dominant pattern was seen in patients with disease duration of more than 20 days.

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