Cytokine levels and pathological characteristics of a patient with severe coronavirus disease 2019: a case report

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To the Editor: The clinical spectrum of coronavirus disease 2019 (COVID-19) appears to be wide, ranging from asymptomatic to severe progressive pneumonia with respiratory failure, multiorgan failure, and even death. Here, we investigated the clinical and pathological characteristics of a patient who died from severe COVID-19. Our findings will facilitate a deeper understanding of the pathogenesis and progression of COVID-19 and improve clinical strategies to combat the disease.

On January 23, 2020, a 57-year-old man without relevant history presented with fatigue and fever after attending a family party 2 days prior. Among the members of the family party, one relative had traveled from Wuhan. Over 9 days, the fever and cough developed, and the patient visited the emergency department. A throat swab was positive for severe acute respiratory syndrome coronavirus 2 (SARS-COV-2) on real-time reverse-transcription polymerase chain reaction. He was admitted to the local hospital and received supportive therapies, anti-viral agents, atomized inhalation of interferon-γ, and oxygen therapy. Cough, fever, and dyspnea further developed on February 8. He received non-invasive mechanical ventilation therapy. On February 18, he was transferred to a superior hospital with shortness of breath. His oxygenation index decreased to 85.8 mmHg, and invasive ventilation was initiated. Comprehensive treatment measures included antibiotic agents, sedative drug injections, vasopressor support, and renal replacement therapy. The next day, his oxygenation index decreased. Extracorporeal membrane oxygenation (ECMO) was initiated. After prone position ventilation for approximately 2 weeks with support from ECMO, his vital signs were still unstable. Severe COVID-19 resulted in leukocytosis and increased levels of inflammatory indicators.[1] Considering the relation between blood cell and the immunologic function, we detected the level of cytokines. The result showed that interleukin (IL)-6: 69.38 pg/mL, IL-10: 32.13 pg/mL. On February 23, we started continuous renal replacement therapy to adsorb endotoxin and cytokines. Laboratory tests revealed that the IL-6 and IL-10 levels were increased (345.51 and 44.77 pg/mL, respectively). Moreover, $CD4^+$ T cell count was 147 cells/μL, and $CD8^+$ T cell count was 114 cells/μL. Also, the lymphocyte count decreased. Lymphopenia is a critical factor associated with disease severity and mortality in patients with COVID-19.[2] The next day, he experienced sudden decreases in his blood pressure and blood oxygenation level, and chest computed tomography images showed right hemopneumothorax. Through thoracoscopy, we observed that the bleeding lobes had formed blood clots. To investigate the pulmonary inflammation, right lung ultrasound guided biopsy was performed on March 16. Histological examination showed that the pathological

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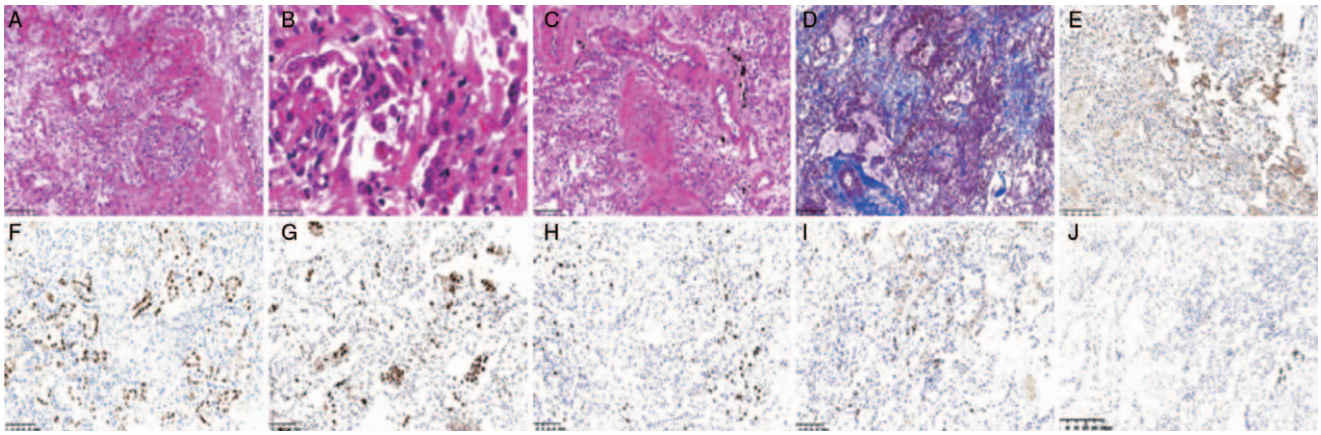

Figure 1: (A) The alveolar structure was destroyed in different degrees, necrosis and exudation were seen in the alveolar cavity (Hematoxylin-eosin [HE] staining, Original magnification ×4). (B) Monocytes, macrophages, individual multinucleated giant cells, and atypical enlarged alveolar cells appear in the alveoli, among which the atypical enlarged alveolar cells have large nuclei, obvious nucleoli, and eosinophilic changes around nucleoli, showing viral cytopathic like changes (HE staining, Original magnification ×20). (C) Alveolar septum thickening, inflammatory cell infiltration, vascular proliferation, dilation, hyperemia, some vascular wall thickening, some vascular lumen occlusion (HE staining, Original magnification ×20). (D) Pulmonary interstitial and perivascular fibrosis in some areas (Masson staining, Original magnification ×20). (E) Immunohistochemical staining showed that the expression of 2019-nCoV nucleoprotein was positive in some alveolar epithelial cells (Original magnification ×20). (F) The increased expression of TTF-1 indicates the proliferation of alveolar epithelial cells (Original magnification ×20). (G) More positive macrophages infiltrated in alveolar septum and alveolar cavity (Original magnification ×20). (H) A small number of $CD8^+$ T cells were found in the alveolar septum and pulmonary interstitium (Original magnification ×20). (I) Spot $CD4^+$ T cells were found in the alveolar septum and pulmonary interstitium (Original magnification ×20). (J) $CD20^+$ B cells were not found in alveolar septum and pulmonary interstitium (Original magnification ×20). 2019-nCoV: 2019-Novel coronavirus; TTF-1: Thyroid transcription factor-1.

changes in the lung tissue varied, including exudative inflammation, interstitial inflammation, and fibrosis in the alveoli; in addition, focal hemorrhaging could be seen. Unfortunately, despite intensive treatment, the patient's immunologic function had not been relieved. The patient died on March 20 [Supplementary Table 1, http://links.lww.com/CM9/A588].

The results of the lung biopsy were similar to those reported in the literature.[3] The varied pathological changes in the lung tissue including exudative inflammation, interstitial inflammation, fibrosis in the alveoli, and focal hemorrhaging were typical manifestations of COVID-19 patients. The alveoli were damaged to different degrees, and some alveoli were filled with cellulose-like exudates and mucus-like substances [Figure 1A]. Type II alveolar epithelial cells had proliferated, and some of them had been shed. There were mononuclear cells, macrophages, individual multinuclear giant cells, and atypical enlarged alveolar epithelial cells in the alveolar cavity. The atypical enlarged alveolar epithelial cells had large nuclei, obvious nucleoli, and eosinophilic changes around the nucleoli, showing viral cytopathic changes [Figure 1B]. No obvious intra-nuclear or cytoplasmic inclusion bodies were found. We found the alveolar septum was widened, inflammatory cells had infiltrated, the blood vessels had proliferated and were dilated and congested, and some blood vessel walls had thickened; no clear thrombus was found in the microvasculature [Figure 1C]. Some areas of alveolar interstitial and perivascular fibrosis were observed [Figure 1D]. The excessive mucus secretion with serous and fibrinous exudation, which could aggravate the dysfunction of ventilation, might be one of the pathogenic mechanisms responsible for the hypoxemia.[4] Immunohistochemical staining showed that 2019-novel coronavirus nucleoprotein was expressed in some alveolar epithelial cells [Figure 1E]. Our studies showed thyroid transcription factor 1 expressed in the proliferative type II alveolar epithelium [Figure 1F]. CD68 is a marker for macrophage activation. There were relatively more CD68-positive macrophages infiltrating the alveolar septum and alveoli [Figure 1G]. A small number of CD8-positive T cells and spot CD4-positive T cells were found in the alveolar septum and pulmonary interstitium, but no CD20-positive B cells were observed [Figure 1H–J].

COVID-19 is a novel identified infectious disease and varied fatality. Cytokines and chemokines are involved in immunity and immunopathology, but a maladjusted immune response may lead to lung injury and a reduced survival rate. SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV) have been known to cause fatal pneumonia associated with elevation levels of pro-inflammatory cytokines and inflammatory cell infiltration.[5] The study showed the presence of increased cytokine levels (IL-6 and IL-10) and lymphopenia ($CD4^+$ and $CD8^+$ T cells) in individuals with severe COVID-19.[6] There were increased concentrations of the highly proinflammatory cytokines IL-6 and IL-10 in the peripheral blood of the patient. We found that the counts of $CD4^+$ and $CD8^+$ T cells were reduced throughout the disease course. Despite an increase in the overall white blood cell count, the $CD4^+$ and $CD8^+$ T cell counts are decreased in severe COVID-19 patients ($P = 0.018$, 0.035, respectively).[7]

COVID-19 has certain commonalities with the pathological changes characteristics of SARS and MERS.[8,9] Infection with these viruses leads to pulmonary edema, pulmonary consolidation, and pulmonary hemorrhage. Microscopically, the lung presents with desquamation alveolitis and exudative lesions in the early stage, extensive hyaline membrane formation, a severe inflammatory reaction, and necrosis. There were many monocyte macrophages in the alveoli of patients with SARS, as well

as positivity for CD68. In patients with MERS, the lungs develop diffuse exudative alveolar damage, alveolar septum destruction and expansion, and type II alveolar epithelial cell proliferation and exfoliation.

Clinical and pathological findings in this patient with severe COVID-19 can help us identify the progression of SARS-CoV-2-related pneumonia. This may be helpful for doctors seeking to develop corresponding treatment strategies for severely ill patients and reduce mortality.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient has given his consent for his images and other clinical information to be reported in the article. The patient understands that his name and initials will not be published and due efforts will be made to conceal the identity of the patient, although anonymity cannot be guaranteed.

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Conflicts of interest

None.

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