Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.
What can we learn from a COVID-19 lung biopsy?

Jinxiang Wu a, 1, Jiguang Yu b, 1, Shengyu Zhou a, Jintao Zhang a, Jiawei Xu a, Chuanzhen Niu b, Guimei Qu c, Bo Han d, Jing Hu a, Liang Dong a, ✉

a Department of Respiratory and Critical Care Medicine, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, 250012, China
b Department of Critical Care Medicine, Yantai Yuhuangding Hospital, Yantai, Shandong, 264001, China
c Department of Pathology, Yantai Yuhan Sleeping University, Yantai, Shandong, 264000, China
d Department of Pathology, Qilu Hospital, Cheeloo College of Medicine, Shandong University, Jinan, Shandong, 250012, China

ARTICLE INFO

Article history:
Received 15 May 2020
Received in revised form 1 July 2020
Accepted 22 July 2020

Keywords:
COVID-19
Lung biopsy
Morphological ultrastructure
Inflammatory biological markers

ABSTRACT

We report the case of a patient diagnosed with severe pneumonia due to coronavirus disease 2019 (COVID-19). A percutaneous lung biopsy was performed under ultrasound guidance. Morphological and ultrastructural characteristics of the patient’s lungs are presented, along with details of some important changes in inflammatory biological markers, in order to help better understand the disease and provide clues to allow members of the multidisciplinary team to save more people.

© 2020 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

Introduction

The newly emerging coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has a significant mortality rate and has spread across nearly the entire world. Although lots of research has been conducted, reports on the pathology of living lung tissue are scarce, due to the limited number of biopsies performed.

In this study, the pathological characteristics of a live patient suffering from severe infection with SARS-CoV-2 were investigated. This study was performed in accordance with the regulations issued by the National Health Commission of China. The study findings will facilitate understanding of the histopathology of COVID-19 and its treatment, and improve clinical strategies against the disease.

Case report

On February 3, 2020, a 55-year-old man was admitted to a fever clinic in Yantai, China, with a 3-day history of high fever, dry cough, fatigue, and shortness of breath. He disclosed that his son had returned to their hometown from epidemic-hit Wuhan on January 21. The patient had taken oral anti-fever medicine, but the fever could not be controlled. His chest computed tomography (CT) showed bilateral multifocal ground glass opacities with consolidation, which suggested viral pneumonia as a differential diagnosis (Figure 1A, B). He was immediately admitted to the isolation ward and received supplemental oxygen through a face mask. On February 4, 2019, nCoV pneumonia nucleic acid testing returned a positive result. Based on real-time reverse transcriptase PCR (rRT-PCR) for SARS-CoV-2, chest CT, and clinical and epidemiological information, the patient received a diagnosis of COVID-19.

The patient had no notable underlying disease before the onset of COVID-19. Physical examination revealed a body temperature of 36.8°C, blood pressure of 134/91 mmHg, pulse of 70 beats per minute, respiratory rate of 23 breaths per minute, and arterial oxygen saturation (SpO2) of 68% while the patient was breathing supplemental oxygen via a mask at 5 l/min. Breathing sounds were initially normal. The laboratory results reflected lymphopenia (6.5%).

A repeat chest CT showed significant progression of the bilateral ground glass opacities in a diffuse distribution, which progressed to ‘white lung’, as shown in Figure 1C. The laboratory results reflected lymphopenia (6.5%) and decreased cellular immunity (CD3+CD4+, 145/µL). A rapid screening test for influenza A and B was negative. Some of the other laboratory

https://doi.org/10.1016/j.ijid.2020.07.067
1201-9712/© 2020 Published by Elsevier Ltd on behalf of International Society for Infectious Diseases. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).
abnormalities identified during routine testing in this case are reported in Table 1, including among others elevated SpO2, lactate, white blood cell count, absolute lymphocyte count, platelet count, oxygen, and carbon dioxide. Despite every effort, the patient’s illness continued to worsen, so a percutaneous lung biopsy under ultrasound guidance was performed at 11 a.m. on day 41 of illness. Unfortunately, the patient died during the night on the same day.

The biopsy specimen was fixed at different times with an interval of 24 h. The first biopsy specimen showed alveolar structure collapse, occlusion, and massive fibrinoid necrosis, and a cellulose exudate could be seen in the residual alveolar space. Alveolar epithelial hyperplasia was evident (Figure 2A). The later lung biopsy specimen showed extensive lung tissue necrosis, most of the alveolar septa were destroyed, the fibrous scaffolds had disappeared, and only a few alveolar structures were preserved; this was accompanied by significant fibrinous exudate and hemorrhage. Necrotic and exfoliated alveolar epithelial cells and chronic inflammatory cells could be seen in the exudates, and the latter was mainly composed of mononuclear cells and lymphocytes. Mucus could be seen in some areas. The walls of the small vessels in the interstitium of the lung showed fibrinoid necrosis (Figure 2B, C). Large amounts of virus were observed by electron microscopy, and the virions were 97–102 nm in diameter (Figure 2D). The later part had high levels of necrosis.

Meanwhile, several important inflammatory markers were also observed. Granulocytes showed strong positive expression of myeloperoxidase (MPO) (Figure 3A), IgG was strongly positively expressed (Figure 3B), and IgD and interleukin (IL)-10 were weakly positively expressed (Figure 3C, D). IL-6 and tumor necrosis factor alpha (TNF-α) were strongly positively expressed (Figure 3E, F); angiotensin-converting enzyme 2 (ACE2) was positively expressed in alveolar epithelial cells (Figure 3G).

### Discussion

So far, few autopsy studies on patients with severe COVID-19 have been reported. In this study, the pathological characteristics of a patient with severe COVID-19 were investigated. The study findings will facilitate understanding of the pathogenesis of COVID-19 and improve clinical strategies against the disease.

Most elderly COVID-19 patients with comorbidities such as hypertension, diabetes, and coronary heart disease are critically ill or die. However, a significant proportion of middle-aged adults with no underlying diseases have also become severely infected, like the patient reported here. In this case, biopsy samples from the lung were taken at the bedside under ultrasound guidance. The later lung biopsy showed extensive lung tissue necrosis; type II alveolar epithelial hyperplasia could be seen and no virus inclusions and multinucleated cells were found. The residual bronchial epithelial cells were found in the local tissue. Due to extensive lung tissue necrosis, there was no alveolar hyaline membrane or other structures.

The pathological features of COVID-19 resemble those seen in severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) (Ding et al., 2003; Ng et al., 2016; Liu et al., 2020). However, the former showed relatively mild damage. The morphological changes in the patient’s lungs conformed to late manifestations of a severe case. The findings indicate that the virus may continue to destroy the lung tissue after the virus has left the body. To some extent, self-degradation and destruction of the tissues cannot be ruled out. Nevertheless, the autopsy results cannot fully represent the patient’s disease status. Virus was also observed in the lung tissue by transmission electron microscopy.
ACE2 is a cell surface protein highly expressed in the lung, kidney, and heart (Turner et al., 2004). SARS-CoV-2 targets the lung and other organs and causes multiorgan damage by binding to the ACE2 receptor (Zhou et al., 2020). Inflammatory cytokines and chemokines, including IL-6 and TNF-α, have been found to be significantly elevated in COVID-19 patients. In the case presented here, expression of ACE2, IL-6, and TNF-α was observed. MPO is a peroxidase mainly produced by granulocytes (neutrophils and tissue monocytes) (Aratani, 2018). The expression of MPO was strongly positive, but neutrophils were scarce in the lung tissue of the patient at that time, suggesting that there may be a large amount of granulocyte infiltration into the lung tissue before and during the middle stage of the disease, resulting in a large amount of MPO production and a local superoxide reaction. In the later stage, the granulocytes may break apart, resulting in MPO accumulation in the lung tissue, which could lead to severe tissue damage (closely related to the oxidative stress response).

According to the pathological findings in the patient with severe COVID-19 presented here, this study not only helped to identify a cause of death, but also facilitates understanding of the pathogenesis of the disease, which might help the multidisciplinary team to formulate a timely therapeutic strategy and reduce mortality for similar severe patient cases.
Funding source

This research was supported by the National Natural Science Foundation of China (grant numbers 26010105201530, 26010105131801, 81770029) and the Key Research Project of Shandong Province (2016GSF201028).

Ethical approval

Ethical approval was obtained from the Qilu Hospital Research Ethics Committee, Shandong University

Conflict of interest

The authors declare no conflict of interest.

References

Aratani Y. Myeloperoxidase: its role for host defense, inflammation, and neutrophil function. Arch Biochem Biophys 2018;640:47–52.

Ding Y, Wang H, Shen H, Li Z, Geng J, Han H, et al. The clinical pathology of severe acute respiratory syndrome (SARS): a report from China. J Pathol 2003;200:282–9.

Liu J, Zheng X, Tong Q, Li W, Wang B, Sutter K, et al. Overlapping and discrete aspects of the pathology and pathogenesis of the emerging human pathogenic coronaviruses SARS-CoV, MERS-CoV, and 2019-nCoV. J Med Virol 2020;92:491–4.

Ng DL, Al Hosani F, Keating MK, Gerber SI, Jones TL, Metcalfe MC, et al. Clinicopathologic, immunohistochemical, and ultrastructural findings of a fatal case of middle east respiratory syndrome coronavirus infection in the United Arab Emirates, April 2014. Am J Pathol 2016;186:652–8.

Turner AJ, Hiscox JA, Hooper NM. ACE2: from vasopeptidase to SARS virus receptor. Trends Pharmacol Sci 2004;25:291–4.

Zhou P, Yang XL, Wang XG, Hu B, Zhang L, Zhang W, et al. A pneumonia outbreak associated with a new coronavirus of probable bat origin. Nature 2020;579:270–3.

Figure 3. Expression of markers in the lung biopsy: (A) myeloperoxidase (MPO); (B) immunoglobulin G (IgG); (C) immunoglobulin D (IgD); (D) interleukin 10 (IL-10); (E) interleukin 6 (IL-6); (F) tumor necrosis factor alpha (TNF-α); (G) angiotensin-converting enzyme 2 (ACE2).