**WORGU VICTORY IZEOMA**

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**ANA 404 HISTOPATHOLOGY**

**INTRODUCTION TO HISTOPATHOLOGY**

* **Aetiology of Covid-19**

Coronaviruses are a family of viruses that can cause illnesses such as the common cold, severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS). In 2019, a new coronavirus was identified as the cause of a disease outbreak that originated in China. The virus is now known as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The disease it causes is called coronavirus disease 2019 (COVID-19). In March 2020, the World Health Organization (WHO) declared the COVID-19 outbreak a pandemic (David, J. Cennimo (2020). Corona virus diseases 2019. *Drugs and diseases<infectious dieseases* <https://doi.org/10.1016/.j.jaut.2020.102433>).

* **Pathogenesis**

Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease that is of great global public health concern. Based on the large number of infected people that were exposed to the wet animal market in Wuhan City, China, it is suggested that this is likely the zoonotic origin of COVID-19. Person-to-person transmission of COVID-19 infection led to the isolation of patients that were subsequently administered a variety of treatments. Extensive measures to reduce person-to-person transmission of COVID-19 have been implemented to control the current outbreak. Special attention and efforts to protect or reduce transmission should be applied in susceptible populations including children, health care providers, and elderly people. In this review, we highlight the symptoms, epidemiology, transmission, pathogenesis, phylogenetic analysis and future directions to control the spread of this fatal disease (David, J. Cennimo (2020). Corona virus diseases 2019. *Drugs and diseases<infectious dieseases* <https://doi.org/10.1016/.j.jaut.2020.102433>).

* **Histopathological Features**

No pathology has been reported due to barely accessible autopsy or biopsy. Here, is a case that was investigated showing the pathological characteristics of a patient who died from severe infection with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by postmortem biopsies. This study was in accordance with regulations issued by the National Health Commission of China and the Helsinki Declaration. The findings facilitated the understanding of the pathogenesis of COVID-19 and improved the clinical strategies against the disease. A 50-year-old man was admitted to a fever clinic on Jan 21, 2020, with symptoms of fever, chills, cough, fatigue and shortness of breath. He reported a travel history to Wuhan Jan 8–12, and that he had initial symptoms of mild chills and dry cough on Jan 14 (day 1 of illness) but did not see a doctor and kept working until Jan 21. On Jan 22 (day 9 of illness), the Beijing Centers for Disease Control (CDC) confirmed by reverse real-time PCR assay that the patient had COVID-19. Chest x-ray showed multiple patchy shadows in both lungs (appendix p 2), and a throat swab sample was taken. He was immediately admitted to the isolation ward and received supplemental oxygen through a face mask. He was given interferon alfa-2b (5 million units twice daily, atomisation inhalation) and lopinavir plus ritonavir (500 mg twice daily, orally) as antiviral therapy, and moxifloxacin (0·4 g once daily, intravenously) to prevent secondary infection. Given the serious shortness of breath and hypoxaemia, methylprednisolone (80 mg twice daily, intravenously) was administered to attenuate lung inflammation. After receiving medication, his body temperature reduced from 39·0 to 36·4 °C. However, his cough, dyspnea, and fatigue did not improve. On day 12 of illness, after initial presentation, chest x-ray showed progressive infiltrate and diffuse gridding shadow in both lungs. He refused ventilator support in the intensive care unit repeatedly because he suffered from claustrophobia; therefore, he received high-flow nasal cannula (HFNC) oxygen therapy (60% concentration, flow rate 40 L/min). On day 13 of illness, the patient's symptoms had still not improved, but oxygen saturation remained above 95%. In the afternoon of day 14 of illness, his hypoxemia and shortness of breath worsened. Despite receiving HFNC oxygen therapy (100% concentration, flow rate 40 L/min), oxygen saturation values decreased to 60%, and the patient had sudden cardiac arrest. He was immediately given invasive ventilation, chest compression, and adrenaline injection. Unfortunately, the rescue was not successful, and he died at 18:31 (Beijing time). Biopsy samples were taken from lung, liver, and heart tissue of the patient. Histological examination showed bilateral diffuse alveolar damage with cellular fibromyxoid exudates. The right lung showed evident desquamation of pneumocystes and hyaline membrane formation, indicating acute respiratory distress syndrome (ARDS). The left lung tissue displayed pulmonary edema with hyaline membrane formation, suggestive of early-phase ARDS. Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterized by large nuclei, amphiphilic granular cytoplasm, and prominent nucleoli were identified in the intra-alveolar spaces, showing viral cytopathic-like changes. No obvious intranuclear or intracytoplasmic viral inclusions were identified. The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection. In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate micro vesicular steatosis and mild lobular and portal activity, indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury. There were a few interstitial mononuclear inflammatory infiltrates, but no other substantial damage in the heart tissue. Peripheral blood was prepared for flow cytometry analysis. They found that the counts of peripheral CD4 and CD8 T cells were substantially reduced, while their status was hyper activated, as evidenced by the high proportions of HLA-DR (CD4 3·47%) and CD38 (CD8 39·4%) double-positive fractions (appendix p 3). Their results imply that over activation of T cells, manifested by increase of Th17 and high cytotoxicity of CD8 T cells, accounts for, in part, the severe immune injury in this patient. X-ray images showed rapid progression of pneumonia and some differences between the left and right lung. There were no obvious histological changes seen in heart tissue, suggesting that SARS-CoV-2 infection might not directly impair the heart (Zhen, X., Lei, S., Yijin, W., Jiyuan Z., Lei, H., Chao Z., *et al* (2020). *Pathological findings of covid-19 associated with acute respiratory distress syndrome*, *8*(4),420-422 <https://doi.org/10.1016/.S2213-2600(20)30076-X)>.

* **Potential Therapies**

The WHO has embarked on an ambitious global "mega trial" called SOLIDARITY in which confirmed cases of COVD-19 are randomized to standard care or one of four active treatment arms (remdesivir, chloroquine or hydroxychloroquine, lopinavir/ritonavir, or lopinavir/ritonavir plus interferon beta-1a) while scientists are evaluating candidate therapies and vaccines to treat and prevent the novel coronavirus.

*Remdesivir:* The broad-spectrum antiviral agent remdesivir (GS-5734; Gilead Sciences, Inc) is a nucleotide analog prodrug. It was studied in clinical trials for Ebola virus infections but showed limited benefit. Remdesivir has been shown to inhibit replication of other human coronaviruses associated with high morbidity in tissue cultures, including severe acute respiratory syndrome coronavirus (SARS-CoV) in 2003 and Middle East respiratory syndrome coronavirus (MERS-CoV) in 2012. Efficacy in animal models has been demonstrated for SARS-CoV and MERS-CoV. Several phase 3 clinical trials are testing remdesivir for treatment of COVID-19 in the United States, South Korea, and China. An adaptive randomized trial of remdesivir coordinated by the National Institute of Health (NCT04280705) was started first against placebo, but additional therapies can be added to the protocol as evidence emerges. The first experience with this study involved passengers of the Diamond Princess cruise ship in quarantine at the University of Nebraska Medical Center after returning to the United States from Japan following an on-board outbreak of COVID-19. Positive results were seen with remdesivir after use by the University of Washington in the first case of COVID-19 documented on US soil. Prophylactic and therapeutic remdesivir improved pulmonary function and reduced lung viral loads and severe lung pathology in mice, whereas LPV/RTV-IFNb slightly reduced viral loads without affecting other disease parameters. Therapeutic LPV/RTV-IFNb improved pulmonary function but did not reduce virus replication or severe lung pathology in the mice.

*Lopinavir/ritonavir:* A combination of lopinavir/ritonavir plus IFNb treatment improved clinical parameters in marmosets and mice infected with MERS-CoV. In a randomized, controlled, open-label trial of hospitalized adults (n=199) with confirmed SARS-CoV-2 infection, recruited patients had an oxygen saturation of 94% or less on ambient air or PaO2 of less than 300 mm Hg and were receiving a range of ventilatory support modes (eg, no support, mechanical ventilation, extracorporeal membrane oxygenation [ECMO].

*Hydroxychloroquine and chloroquine:* Hydroxychloroquine and chloroquine are widely used antimalarial drugs that elicit immunomodulatory effects and are therefore also used to treat autoimmune conditions (eg, systemic lupus erythematosus, rheumatoid arthritis). As inhibitors of heme polymerase, they are also believed to have additional antiviral activity via alkalization of the phagolysosome, which inhibits the pH-dependent steps of viral replication. Wang et al reported that chloroquine effectively inhibits SARS-CoV-2 in vitro. The pharmacological activity of chloroquine and hydroxychloroquine was tested using SARS-CoV-2–infected Vero cells. Hydroxychloroquine was found to be more potent than chloroquine in vitro.

*Corticosteroids:* Corticosteroids are not generally recommended for treatment of COVID-19 or any viral pneumonia. The benefit of corticosteroids in septic shock results from tempering the host immune response to bacterial toxin release. The incidence of shock in patients with COVID-19 is relatively low (5% of cases). It is more likely to produce cardiogenic shock from increased work of the heart need to distribute oxygenated blood supply and thoracic pressure from ventilation. Corticosteroids can induce harm through immunosuppressant effects during the treatment of infection and have failed to provide a benefit in other viral epidemics, such as respiratory syncytial virus (RSV) infection, influenza infection, SARS, and MERS.

*Convalescent plasma:* The FDA is facilitating access to convalescent plasma, antibody-rich products that are collected from eligible donors who have recovered from COVID-19. Convalescent plasma has not yet been shown to be effective in COVID-19. The FDA states that it is important to determine its safety and efficacy via clinical trials before routinely administering convalescent plasma to patients with COVID-19.

*Nitric oxide:* Published findings from the 2004 SARS-CoV infection suggest the potential role of inhaled nitric oxide as a supportive measure for treating infection in patients with pulmonary complications. Treatment with iNO reversed pulmonary hypertension, improved severe hypoxia, and shortened the length of ventilatory support compared with matched control patients with SARS.

*Statins:* In addition to the cholesterol-lowering abilities of HMG-CoA reductase inhibitors (statins), they also decrease the inflammatory processes of atherosclerosis. Because of this, questions have arisen whether statins may be beneficial to reduce inflammation associated with COVID-19

(Scott, J. Bergman (2020). Treatment of corona virus: investigational drugs and other therapies. *Drugs and diseases> infectious diseases*  <https://emedicine.medscape.com>).

* **The Future of Covid-19 on Public Health**

The COVID-19 pandemic will transform the global health community’s acceptance and use of digital health technologies. As health systems around the world are overwhelmed responding to COVID-19 while continuing to provide health care services, leaders are adopting technologies that only three months ago were on the sidelines of most health care systems. As doctors, patients and home care providers turn to telemedicine to reduce exposure to COVID-19, they are discovering these virtual consultations are effective for triaging care, sharing critical guidance, and providing emotional support. More advanced technologies are being employed to provide insights into complex questions of how individual behaviors impact transmission and identifying which policies are effective for specific groups. Once deployed, the use of these technologies will only expand as we revert back to solving the challenges problems that preoccupied us prior to COVID-19. Too few health personnel, inadequate budgets, and weak health systems will be worked on because of the pandemic. Maybe these technologies will be what helps us get closer to our shared goal of universal health coverage. “COVID-19 could be what makes us finally deliver on the promises of remote learning and support, impacts that will serve health workers, particularly in rural areas long after this pandemic ends. Then looking towards monetary/investment sector the COVID-19 pandemic demands rapid responses. The health sector and general public will be forced to learn quickly about what works. Some responses to the COVID-19 pandemic will be more effective than others in terms of investments. In moving fast and learning fast, we’ll strengthen the muscles we as a community need to respond to the uncertain environments that are an inevitable part of our work going forward. Before the pandemic, the global health and development community has had to stretch its resources to meet global challenges and life-saving commodities have been underfunded. Now, resources are likely to be more constrained than ever. Inefficient and wasteful spending will be even more noticeable during this crisis. This pandemic will force us to articulate what matters most and to prioritize investments most especially in the health sector in provision of technologies and equipment needed. This pandemic will force a reexamination of global health architecture to promote an approach to sustainability that significantly increases investment in emergency preparedness with an eye to how that investment supports, but does not supplant, “regular order” service delivery. COVID-19 has put greater value on data, research, and epidemiological surveillance on things regularly used in public health, now supercharged to inform a pandemic response. Additionally, COVID-19 has revealed the need to manufacture health commodities and strengthen supply chains closer to where materials are needed domestically and globally (http://devex.com).