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**ANATOMY, 400L**

**HISTOPATHOLOGY ASSIGNMENT**

**INTRODUCTION**

Coronavirus is one of the major pathogens that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the severe acute respiratory syndrome (SARS)-CoV and the Middle East respiratory syndrome (MERS)-CoV which have been previously characterized as agents that are a great public health threat. In late December 2019, a cluster of patients was admitted to hospitals with an initial diagnosis of pneumonia of an unknown etiology. These patients were epidemiologically linked to a seafood and wet animal wholesale market in Wuhan, Hubei Province, China (Bogoch *et al.*, 2020; Lu *et al., 2020)*. Early reports predicted the onset of a potential Coronavirus outbreak given the estimate of a reproduction number for the 2019 Novel (New) Coronavirus (COVID-19, named by WHO on Feb 11, 2020) which was deemed to be significantly larger than 1 (ranges from 2.24 to 3.58) (Zhao *et al., 2020)*.

 The chronology of COVID-19 infections is as follows. The first cases were reported in December 2019 (Du Toit *et al., 2020)*. From December 18, 2019 through December 29, 2019, five patients were hospitalized with acute respiratory distress syndrome and one of these patients died (Ren *et al.,*2020).

By January 2, 2020, 41 admitted hospital patients had been identified as having laboratory-confirmed COVID-19 infection, less than half of these patients had underlying diseases, including diabetes, hypertension and cardiovascular disease (Huang *et al.,* 2020). These patients were presumed to be infected in that hospital, likely due to nosocomial infection. It was concluded that the COVID-19 is not a super-hot spreading virus (spread by one patient to many others), but rather likely spread due to many patients getting infected at various locations throughout the hospital through unknown mechanisms. In addition, only patients that got clinically sick were tested, thus there were likely many more patients that were presumably infected. As of January 22, 2020, a total of 571 cases of the 2019-new coronavirus (COVID-19) were reported in 25 provinces (districts and cities) in China (Lu *et al., 2020)*

The China National Health Com- mission reported the details of the first 17 deaths up to January 22, 2020. On January 25, 2020, a total of 1975 cases were confirmed to be infected with the COVID-19 in mainland China with a total of 56 deaths (Wang *et al., 2020)*. Another report on January 24, 2020 estimated the cumulative incidence in China to be 5502 cases (Nishiura *et al., 2020)*. As of January 30, 2020, 7734 cases have been confirmed in China and 90 other cases have also been reported from a number of countries that include Taiwan, Thailand, Vietnam, Malaysia, Nepal, Sri Lanka, Cambodia, Japan, Singapore, Republic of Korea, United Arab Emirates, United States, The Philippines, India, Australia, Canada, Finland, France, and Germany. The case fatality rate was calculated to be 2.2% (170/7824) (Bassetti *et al.,* 2020).

**AETIOLOGY OF COVID-19**

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is a previously unknown (Nicholas *et al.,* 2020) betacoronavirus that was discovered in bronchoalveolar lavage samples taken from clusters of patients who presented with pneumonia of unknown cause in Wuhan City, Hubei Province, China, in December 2019 (Nicholas *et al.,* 2020). Coronaviruses are a large family of enveloped RNA viruses, some of which cause illness in people (e.g., common cold, severe acute respiratory syndrome [SARS], Middle East respiratory syndrome [MERS]), and others that circulate among mammals and birds. Rarely, animal coronaviruses can spread to humans and subsequently spread between people, as was the case with SARS and MERS (Nicholas *et al.,* 2020)

SARS-CoV-2 belongs to the Sarbecovirus subgenus of the Coronaviridae family, and is the seventh coronavirus known to infect humans. The virus has been found to be similar to SARS-like coronaviruses from bats, but it is distinct from SARS-CoV and MERS-CoV. The full genome has been determined and published in GenBank (Nicholas *et al.,* 2020)

**Origin of virus**

 A majority of patients in the initial stages of this outbreak reported a link to the Huanan South China Seafood Market, a live animal or ‘wet’ market, suggesting a zoonotic origin of the virus (Nicholas *et al.,* 2020). While the potential animal reservoir and intermediary host(s) are unknown at this point, studies suggest they may derive from a recombinant virus between the bat coronavirus and an origin-unknown coronavirus; however, this is yet to be confirmed. Pangolins have been suggested as an intermediate host as they have been found to be a natural reservoir of SARS-CoV-2-like coronaviruses. Transmission dynamics (Nicholas *et al.,* 2020)

 Person-to-person spread has been confirmed in community and healthcare settings, with local transmission now occurring in many countries around the world (Nicholas *et al.,* 2020)

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 ([Rothan and](https://www.ncbi.nlm.nih.gov/pubmed/?term=Rothan%20HA%5BAuthor%5D&cauthor=true&cauthor_uid=32113704) [Byrareddy,](https://www.ncbi.nlm.nih.gov/pubmed/?term=Byrareddy%20SN%5BAuthor%5D&cauthor=true&cauthor_uid=32113704) 2020)

 An initial assessment of the transmission dynamics in the first 425 confirmed cases found that 55% of cases before 1 January 2020 were linked to the Huanan South China Seafood Market, whereas only 8.6% of cases after this date were linked to the market. This confirms that person-to-person spread occurred among close contacts since the middle of December 2019, including infections in healthcare workers (Nicholas *et al.,* 2020)

It is uncertain how easily the virus spreads between people, but transmission in chains involving several links is increasingly recognized. Available evidence indicates that human transmission occurs via close contact with respiratory droplets produced when a person exhales, sneezes, or coughs; via direct contact with infected people; or via contact with fomites. Airborne transmission has not been reported; however, it may be possible during aerosol-generating procedures performed in clinical care (Nicholas *et al.,* 2020)

The virus has been found to be more stable on plastic and stainless steel (up to 72 hours) compared with copper (up to 4 hours) and cardboard (up to 24 hours).[27] This study also found that the virus was viable in aerosol particles for up to 3 hours; however, aerosols were generated using highpowered apparatus that do not reflect normal human cough conditions or a clinical setting where aerosol-generating procedures are performed. The World Health Organization has confirmed that there have been no reports of airborne transmission (Nicholas *et al.,* 2020)

The contribution to transmission by the presence of the virus in other body fluids is unknown; however, the virus has been detected in blood, cerebrospinal fluid, saliva, tears, and conjunctival secretions. Faecal-oral transmission may be possible (virus has been detected in the stool samples of almost half of the patients in one meta-analysis), although it has not been reported yet (Nicholas *et al.,* 2020)

**SYMPTOMS**

The symptoms of COVID-19 infection appear after an incubation period of approximately 5.2 days ( Li *et al., 2020)*. The period from the onset of COVID-19 symptoms to death ranged from 6 to 41 days with a median of 14 days ( Wang *et al., 2020).* This period is dependent on the age of the patient and status of the patient's immune system. It was shorter among patients > 70-years old compared with those under the age of 70 ( Wang *et al., 2020).* The most common symptoms at onset of COVID-19 illness are fever, cough, and fatigue, while other symptoms include sputum production, head- ache, haemoptysis, diarrhoea, dyspnoea, and lymphopenia ( Ren *et al*., 2020; Huang *et al.,* 2020; Wang *et al*., 2020; Carlos *et al., 2020)*. Clinical features revealed by a chest CT scan presented as pneumonia, however, there were abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of grand-glass opacities that led to death ( Huang *et al., 2020).* In some cases, the multiple peripheral ground-glass opacities were observed in subpleural regions of both lungs ( Lei *et al., 2020)* that likely induced both systemic and localized immune response that led to increased inflammation. Regrettably, treat- ment of some cases with interferon inhalation showed no clinical effect and instead appeared to worsen the condition by progressing pulmonary opacities (Lei *et al.,* 2020]

**PATHOGENESIS OF COVID-19**

Patients with COVID-19 show clinical manifestations include fever, nonproductive cough, dyspnea, myalgia, fatigue, normal or decreased leukocyte counts, and radiographic evidence of pneumonia (Xiaowei *et al.,* 2020). which are similar to the symptoms of SARS-CoV and MERS-CoV infections (Xiaowei *et al.,* 2020). Hence, although the pathogenesis of COVID-19 is poorly understood, the similar mechanisms of SARS-CoV and MERS-CoV still can give us a lot of information on the pathogenesis of SARS-CoV-2 infection to facilitate our recognition of COVID-19 (Xiaowei *et al.,* 2020)

**Coronavirus entry and replication**

Coronavirus S protein has been reported as a significant determinant of virus entry into host cells. The envelope spike glycoprotein binds to its cellular receptor, ACE2 for SARS-CoV and SARS-CoV-2, CD209L a C-type lectin, also called L-SIGN) for SARS-CoV, DPP4 for MERS CoV(Xiaowei *et al.,* 2020). The entry of SARS-CoV into cells was initially identiﬁed to be accomplished two-step furin activation for membrane fusion. Besides membrane fusion, the clathrin-dependent and -independent endocytosis mediated SARS-CoV entry too. After the virus enters the cells, the viral RNA genome is releaseed into the cytoplasm and is translated into two polyproteins and structural proteins, after which the viral genome begins to replicate. The newly formed envelope glycoproteins are inserted into the membrane of the endoplasmic reticulum or Golgi, and the nucleocapsid is formed by the combination of genomic RNA and nucleocapsid protein. Then, viral particles germinate into the endoplasmic reticulum-Golgi intermediate compartment (ERGIC). At last, the vesicles containing the virus particles then fuse with the plasma membrane to release the virus (Xiaowei *et al.,* 2020)

**Antigen presentation in coronavirus infection**.

While the virus enters the cells, its antigen will be presented to the antigen presentation cells (APC), which is a central part of the body's anti-viral immunity (Xiaowei *et al.,* 2020). Antigenic peptides are presented by major histocompatibility complex (MHC; or human leukocyte antigen (HLA) in humans) and then recognized by virus-specific cytotoxic T lymphocytes (CTLs). Hence, the understanding of antigen presentation of SARS-CoV-2 will help our comprehension of COVID-19 pathogenesis. Unfortunately, there is still lack of any report about it, and we can only get some information from previous researches on SARS CoV and MERS-CoV (Xiaowei *et al.,* 2020) The antigen presentation of SARS-CoV mainly depends on MHC I molecules, but MHC II also contributes to its presentation. Previous research shows numerous HLA polymorphisms correlate to the susceptibility of SARS-CoV, such as HLA-B 4601, HLA-B 0703, HLA-DR B1 and HLA-Cw0801, whereas the HLA-DR0301, HLA-Cw1502 and HLA-A 0201 alleles are related to the protection from SARS infection. In MERS-CoV infection, MHC II molecules, such as HLA-DRB111:01 and HLA-DQB102:0, are associated with the susceptibility to MERS-CoV infection. Besides, gene polymorphisms of MBL (mannose-binding lectin) associated with antigen presentation are related to the risk of SARS-CoV infection. These researches will provide valuable clues for the prevention, treatment, and mechanism of COVID-19 (Xiaowei *et al.,* 2020)

**Humoral and cellular immunity**

Antigen presentation subsequently stimulates the body's humoral and cellular immunity, which are mediated by virus-specific B and T cells (Xiaowei *et al.,* 2020). Similar to common acute viral infections, the antibody profile against SARS-CoV virus has a typical pattern of IgM and IgG production. The SARS-specific IgM antibodies disappeared at the end of week 12, while the IgG antibody can last for a long time, which indicates IgG antibody may mainly play a protective role, and the SARS-specific IgG antibodies primarily are S-specific and N-specific antibodies.Comparing to humoral responses, there are more researches on the cellular immunity of coronavirus. The latest report shows the number of CD4 + and CD8+ T cells in the peripheral blood of SARS-CoV-2-infected patients significantly is reduced whereas its status is excessive activation, as evidenced by high proportions of HLA-DR (CD4 3.47%) and CD38 (CD8 39.4%) double-positive fractions. Similarly, the acute phase response in patients with SARS-CoV is SARS-CoV infection, specific T-cell memory responses to the SARS-CoV S peptide library could still be identified in 14 of 23 recovered SARS patients. The specific CD8 + T cells also show a similar effect on MERS-CoV clearance in mice. These findings may provide valuable information for the rational design of vaccines against SARS-CoV-2.

**Cytokine storm in COVID-19**

The report in Lancet shows ARDS is the main death cause of COVID-19. Of the 41 SARS-CoV-2-infected patients admitted in the early stages of the outbreak, six died from ARDS (Xiaowei *et al.,* 2020). ARDS is the common immunopathological event for SARS-CoV-2, SARS-CoV and MERS-CoV infections. One of the main mechanisms for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α, TGFβ, etc.) and chemokines (CCL2, CCL3, CCL5, CXCL8, CXCL9, CXCL10, etc.) by immune effector cells in SARS-CoV infection. Similar to those with SARS-CoV, individuals with severe MERS-CoV infection show elevated levels of IL-6, IFN-α, and CCL5, CXCL8, CXCL-10 in serum compared to those with the mild-moderate disease. The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection, just like what occurs in SARS-CoV and MERS-CoV infection (Xiaowei *et al.,* 2020)

**Coronavirus immune evasion**

To better survive in host cells, SARS-CoV and MERS-CoV use multiple strategies to avoid immune responses. The evolutionarily conserved microbial structures called pathogen-associated molecular patterns (PAMPs) can be recognized by pattern recognition receptors (PRRs) (Xiaowei *et al.,* 2020). However, SARS-CoV and MERS-CoV can induce the production of double-membrane vesicles that lack PRRs and then replicate in these vesicles, thereby avoiding the host detection of their dsRNA. IFN-I (IFN-α and IFN-β) has a protective effect on SARS-CoV and MERS-CoV infection, but the IFN-I pathway is inhibited in infected mice. Accessory protein 4a of MERS-CoV may block the induction of IFN at the level of MDA5 activation through direct interaction with double-stranded RNA. Besides, ORF4a, ORF4b, ORF5, and membrane proteins of MERS-CoV inhibit nuclear transport of IFN regulatory factor 3 (IRF3) and activation of IFN β promoter (Xiaowei *et al.,* 2020). The antigen presentation can also be affected by the coronavirus. For example, gene expression related to antigen presentation is down-regulated after MERS-CoV infection. Therefore, destroying the immune evasion of SARS-CoV-2 is imperative in its treatment and specific drug development (Xiaowei *et al.,* 2020)

**HISTOPATTHOLOGY OF COVID-19**

The pathological features of COVID-19 greatly resemble those seen in SARS and Middle Eastern respiratory syndrome (MERS) coronavirus infection (Zhe Xu *et al.,* 2020). In addition, the liver biopsy specimens of the patient with COVID-19 showed moderate microvesicular steatosis and mild lobular and portal activity (Zhe Xu *et al.,* 2020), indicating the injury could have been caused by either SARS-CoV-2 infection or drug-induced liver injury (Zhe Xu *et al.,* 2020).

There was a reduction in the counts of peripheral CD4 and CD8 T cells, while their status was hyperactivated, as evidenced by the high proportions of HLA-DR (CD4 3·47%) and CD38 (CD8 39·4%) double-positive fractions (Zhe Xu *et al.,* 2020). Moreover, there was an increased concentration of highly proinflammatory CCR6+ Th17 in CD4 T cells Additionally, CD8 T cells were found to harbour high concentrations of cytotoxic granules, in which 31·6% cells were perforin positive, 64·2% cells were granulysin positive, and 30·5% cells were granulysin and perforin double-positive (Zhe Xu *et al.,* 2020) Our results imply that overactivation 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.

Although corticosteroid treatment is not routinely recommended to be used for SARS-CoV-2 pneumonia (Zhe Xu *et al.,* 2020), according to our pathological findings of pulmonary oedema and hyaline membrane formation, timely and appropriate use of corticosteroids together with ventilator support should be considered for the severe patients to prevent ARDS development. Lymphopenia is a common feature in the patients with COVID-19 and might be a critical factor associated with disease severity and mortality (Zhe Xu *et al.,* 2020). Our clinical and pathological findings in this severe case of COVID-19 can not only help to identify a cause of death, but also provide new insights into the pathogenesis of SARS-CoV-2-related pneumonia, which might help physicians to formulate a timely therapeutic strategy for similar severe patients and reduce mortality (Zhe Xu *et al.,* 2020).

**CURRENT POTENTIAL THERAPIES AND THE FUTURE OF COVID-19**

There is [no proof that any drug can cure or prevent infection](https://www.cdc.gov/coronavirus/2019-ncov/hcp/therapeutic-options.html) with the coronavirus (Denise et al., 2020). But in the face of an exploding pandemic with a frightening death toll, people are desperate for a bit of hope, a chance to believe there is something that will help (Denise et al., 2020).

The drug that has received the most attention is hydroxychloroquine, which [President Trump has recommended repeatedly](https://www.nytimes.com/2020/04/06/us/politics/coronavirus-trump-malaria-drug.html), despite warnings from his own health officials that there is little data to support its widespread use as a treatment against the virus (Denise et al., 2020)

Drug companies across the world have begun donating tens of millions of doses of hydroxychloroquine to the United States, and the president said on April 4 that 29 million doses had been added to the National Strategic Stockpile, a cache of medical supplies maintained by the government to respond to emergencies (Denise et al., 2020)

It has been reported that Chloroquine can be used to treat COVID-19, however, the cure is not yet found. People have been dying especially the elderly and children, but the adults have more chance of survival, and only those whose immune system is functioning accurately survive. Bill Gates predicted virus as the future of war because it has no cure for now, but only treatment (Denise et al., 2020)

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