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**16/MHS01/145**

**ANA 404**

 **INTRODUCTION TO HISTOPATHOLOGY**

# The Aetiology of COVID-19

**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) 7*.

 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). The first case of COVID-19 infection confirmed in the United States led to the description, identification, diagnosis, clinical course, and management of this case.

**Virological characteristics of SARS-CoV-2**

 SARS-CoV-2 is the causative pathogen of COVID-19, identified as the seventh type of coronavirus to infect humans (Zhu *et al.,* 2020). Six other kinds of coronaviruses are known to cause human disease, including severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle East respiratory syndrome coronavirus (MERS-CoV) with high mortality rate (Su *et al., 2016)*. According to the genome characteristics, coronavirus is separated into four genera: α-CoV, β-CoV, γ-CoV, and δ-CoV (Su *et al.,* 2016). Deep sequencing revealed that this novel coronavirus isolated from lower respiratory tract samples of patient with COVID-19 belongs to β-CoV (Zhu *et al., 2020)*.

 Coronavirus has the appearance of crown under electron microscopy. They are enveloped viruses with a single- strand, positive-sense RNA genome, which is the largest known genome for an RNA virus (Forni *et al., 2017*). All coronaviruses share the same genome organization and expression pattern, with two large overlapping reading frames (ORF1a/b) which encode 16 nonstructural proteins, followed by ORFS for four major structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Forni *et al., 2017)*. The SARS-CoV-2 protein also contains eight accessory proteins (Wu *et al., 2020*). Spike protein plays an essential role in binding to receptors and is critical for determining host tropism and transmission capacity. It is functionally divided into S1 domain and S2 domain, responsible for receptor binding and cell membrane fusion respectively. The receptor binding domain (RBD) of β-CoV is commonly located in the C-terminal domain of S1 (Lu *et al.,*2020)15. A team analyzed the cryogenic electron microscopy (Cryo- EM) structure of the SARS-CoV-2 spike protein and found that it has 10 to 20-fold higher binding affinity to human angiotensin-converting enzyme 2 (ACE2) than SARS- CoV does (Wrapp *et al., 2020)*.

 Phylogenetic analysis of the evolution history showed that SARS-CoV-2 shared a closer sequence homology toward the genomes of SARS-CoV than to that of MERS-CoV ( Xu *et al., 2020)*. SARS-CoV-2 is highly similar to a bat coronavirus RaTG13, with an overall genome sequence identity of 96.2% (Zhou *et al.,*2020), indicating that bat, which was discovered to be the natural reservoir host of various SARS-related coronaviruses ( de Wit *et al., 2016)*, may also be the original host of SARS-CoV-2. The intermediate host in the process of transmission remains uncertain.

**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**

 The severe symptoms of COVID-19 are associated with an increasing numbers and rate of fatalities specially in the epidemic region of China. On January 22, 2020, the China National Health Commission reported the details of the first 17 deaths and on January 25, 2020 the death cases increased to 56 deaths ( Wang *et al., 2020).*  The percentage of death among the reported 2684 cases of COVID-19 was approximately 2.84% as of Jan 25, 2020 and the median age of the deaths was 75 (range 48–89) years (Wang *et al.,* 2020).

 Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-in- flammatory cytokines. One of the COVID-19 case reports showed a patient at 5 days of fever presented with a cough, coarse breathing sounds of both lungs, and a body temperature of 39.0 °C. The patient's sputum showed positive real-time polymerase chain reaction results that confirmed COVID-19 infection (Lei *et al.,* 2020). The laboratory studies showed leucopenia with leukocyte counts of 2.91 × 10^9 cells/L of which 70.0% were neutrophils. Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L). High erythrocyte sedimentation rate and D-dimer were also observed (Lei *et al.,* 2020).

 The main pathogenesis of COVID-19 infection as a respiratory system targeting virus was severe pneumonia, RNAaemia, combined with the incidence of ground-glass opacities, and acute cardiac injury (Huang *et al.,* 2020). Significantly high blood levels of cytokines and che mokines were noted in patients with COVID-19 infection that included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA. Some of the severe cases that were admitted to the intensive care unit showed high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα that are reasoned to promote disease severity (Huang *et al.,* 2020).

**HISTOPATHOLOGICAL FINDINGS**



***Figure 2: Pathological manifestations of right (A) and left (B) lung tissue, liver tissue (C), and heart tissue (D) in a patient with severe pneumonia caused by SARS-CoV-2***

***SARS-CoV-2=severe acute respiratory syndrome coronavirus 2.***

Biopsy samples were taken from lung, liver, and heart tissue of a 50-year-old COVID-19 patient. Histological examination showed bilateral diffuse alveolar damage with cellular bromyxoid exudates ( figure 2A, B). The right lung showed evident desquamation of pneumocytes and hyaline membrane formation, indicating acute respiratory distress syndrome (ARDS; figure 2A). The left lung tissue displayed pulmonary oedema with hyaline membrane formation, suggestive of early-phase ARDS ( figure 2B). Interstitial mononuclear inflammatory infiltrates, dominated by lymphocytes, were seen in both lungs. Multinucleated syncytial cells with atypical enlarged pneumocytes characterised by large nuclei, amphophilic 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. (Wu *et al*., 2020; Huang *et al.,* 2020; Chan *et al.,* 2020; Ding *et al., 2003).*

**Therapeutics/treatment options**

 The person-to-person transmission of COVID-19 infection led to the isolation of patients that were administered a variety of treatments. At present, there are no specific antiviral drugs or vaccine against COVID- 19 infection for potential therapy of humans. The only option available is using broad-spectrum antiviral drugs like Nucleoside analogues and also HIV-protease inhibitors that could attenuate virus infection until the specific antiviral becomes available (Lu *et al., 2020).* The treatment that have so far been attempted showed that 75 patients were administrated existing antiviral drugs. The course of treatment included twice a day oral ad- ministration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0·25 g ganciclovir for 3–14 days (Chen *et al*., 2020). Another report showed that the broad-spectrum antiviral remdesivir and chloroquine are highly effective in the control of 2019- nCoV infection in vitro. These antiviral compounds have been used in human patients with a safety track record. Thus, these therapeutic agents can be considered to treat COVID-19 infection (Wang *et al.,* 2020). Further- more, there are a number of other compounds that are in development. These include the clinical candidate EIDD-2801 compound that has shown high therapeutic potential aganist seasonal and pandemic in- fluenza virus infections and this represents another potential drug to be considered for the treatment of COVID-19 infection (Toots *et al.,* 2019). Along those lines, until more specific therapeutics become available, it is reasonable to consider more broad-spectrum antivirals that provide drug treatment options for COVID-19 infection include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), RNA synthesis inhibitors. It is clear however, that more research is urgently needed to identify novel che- motherapeutic drugs for treating COVID-19 infections. In order to develop pre-and post-exposure prophylaxis against COVID-19, there is an urgent need to establish an animal model to replicate the severe disease currently observed in humans. Several groups of scientists are currently working hard to develop a nonhuman primate model to study COVID- 19 infection to establish fast track novel therapeutics and for the testing of potential vaccines in addition to providing a better understanding of virus-host interactions.

**Future directions to control the spread of the disease**

 Extensive measures to reduce person-to-person transmission of COVID-19 are required 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. A guideline was published for the medical staff, healthcare providers, and, public health individuals and researchers who are interested in the 2019-nCoV (Jin *et al.,* 2020). The early death cases of COVID-19 outbreak occurred primarily in elderly people, possibly due to a weak immune system that permits faster progression of viral infection (Wang *et al.,* 2020; Li *et al., 2020)*. The public services and facilities should provide de- contaminating reagents for cleaning hands on a routine basis. Physical contact with wet and contaminated objects should be considered in dealing with the virus, especially agents such as faecal and urine samples that can potentially serve as an alternative route of transmission (Assiri *et al.,* 2013; Lee *et al.,* 2003). China and other countries including the US have implemented major prevention and control measures including travel screenings to control further spread of the virus (Carlos *et al., 2020)*.

 Epidemiological changes in COVID-19 infection should be monitored taking into account potential routes of transmission and subclinical infections, in addition to the adaptation, evolution, and virus spread among humans and possible intermediate animals and reservoirs. There remains a considerable number of questions that need to be addressed. These include, but are not limited to, details about who and how many have been tested, what proportion of these turned positive and whether this rate remains constant or variable. Very few paediatric cases have so far been reported; is this due to lack of testing or a true lack of infection/sus- ceptibility? Of the ones that have so far been tested, how many have developed severe disease and how many were tested positive but showed no clinical sign of disease? There are some basic questions that would provide a framework for which more specific and detailed public health measures can be implemented.

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