Pathogenesis of COVID-19

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ABSTRACT

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has resulted in a world-wide pandemic of COVID-19 respiratory disease. This paper outlines the symptoms, stages of disease progression, known transmission paths, pathogenesis, and possible treatments as reported in the current scientific literature.

(Keywords: Coronavirus, COVID-19, SARS, Severe Acute Respiratory Syndrome, pathogenesis, virus, global pandemic).

INTRODUCTION

In December 2019, a virus now named as the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) created a series of atypical respiratory diseases originating in Wuhan, Hubei Province, China [1]. This virus created a disease known as COVID-19. It is believed that the outbreak originally started via a zoonotic transmission associated with exposure to the wet animal market in Wuhan City [2].

The pandemic of COVID-19 spread rapidly, creating great global public health concern. It has impacted a large number of people worldwide, being reported in approximately 200 countries and territories [2]. Due to the person-to-person transmission of COVID-19, infected patients were led into isolation while being administered a variety of treatments. Many extensive measurements have been introduced in order to reduce person-to-person transmission, particularly to protect susceptible populations such as the elderly [2]. The management of COVID-19 has been incredibly difficult due to numerous reasons, including the high infectivity of the virus, large asymptomatic populations, and lack of ineffective antivirals and vaccines [3]. The knowledge related to the pathobiology of this disease is quite limited and in order to reach acceptable conclusions, previous knowledge related to SARS-CoV must be utilized [1].

SYMPTOMS

On average, the symptoms of COVID-19 appear after an incubation period of approximately 5.2 days [4]. Some of the most common symptoms include fever, cough, fatigue headaches, diarrhea, hemoptysis, dyspnea, and lymphopenia [5]. There have been some general similarities in the symptoms between COVID-19 and the previous betacoronavirus. However, COVID-19 has shown some unique clinical features, which includes the focus on lower airways, explaining the upper respiratory tract symptoms [3]. These symptoms include rhinorrhea, sneezing, and sore throat [3] (Figure 1). To add on, previous coronaviruses did not exhibit intestinal symptoms such as diarrhea, while a larger percentage of patients infected with COVID-19 did [3].

Some similarities between COVID-19 and the earlier betacoronavirus include fever, dry cough, dyspnea and bilateral ground-glass opacities as seen on chest CT scans [3]. The period from the onset of COVID-19 symptoms to the patient's death ranged from 6 to 41 days, with a median of 14 days [5]. This period is dependent on various factors, including the patient's immune system and their age [3]. This period was shorter for patients over the age of 70 years old compared to those that were younger [5]. By looking at the cells that are likely infected, COVID-19 can be divided into three phases that correspond to the different clinical stages of the disease.

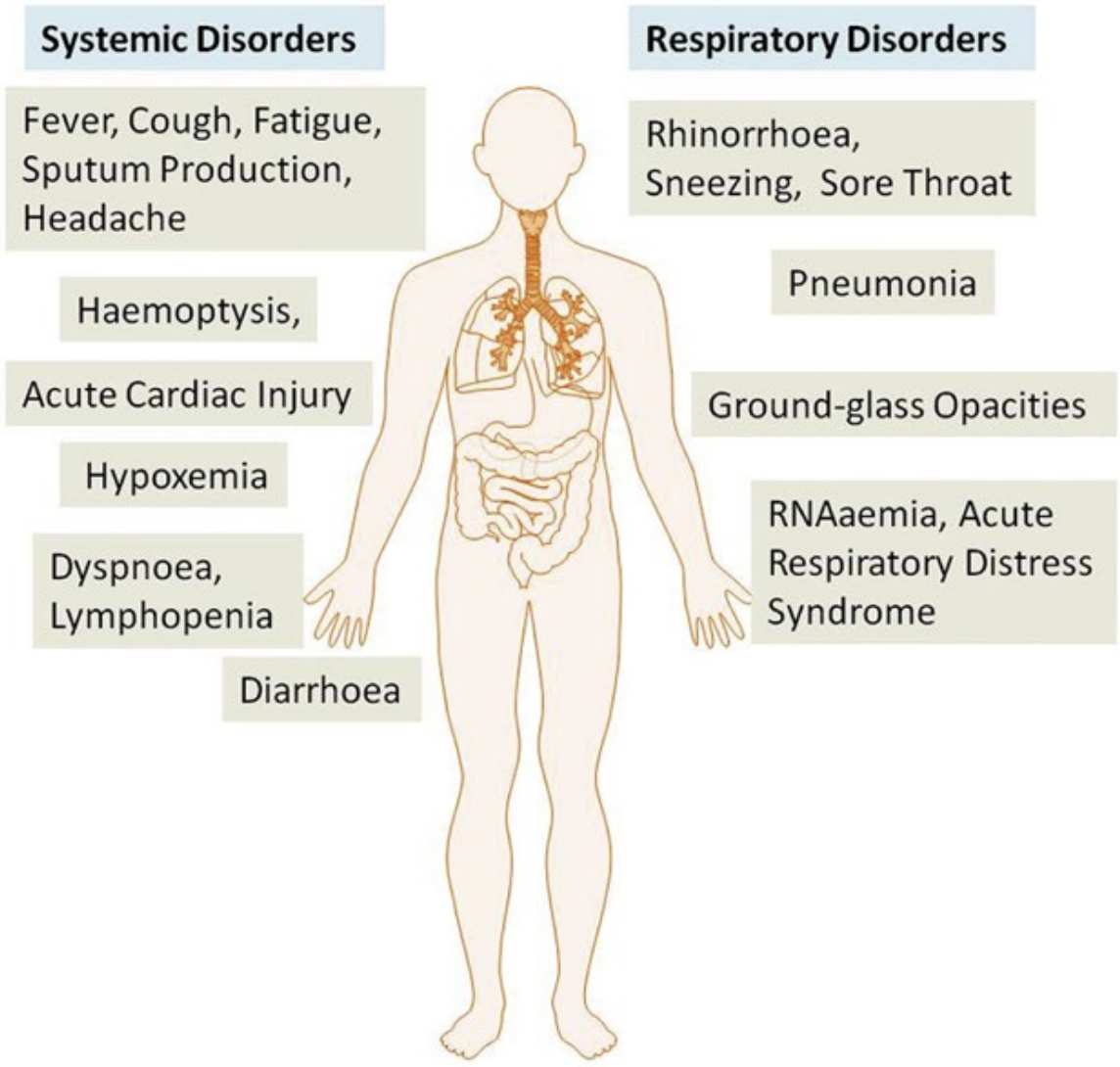

Figure 1: Systemic and Respiratory Disorders Associated with COVID-19 Infection.

Figure 1 shows the systemic and respiratory disorders caused by COVID-19 infection. A chest CT scan revealed abnormal features such as RNAaemia, acute respiratory distress syndrome, acute cardiac injury, and incidence of ground-glass opacities, which led to death in some cases [3]. In some patients, the multiple peripheral ground-glass opacities were seen in subpleural regions of both lungs, including an immune response and leading to increased inflammation [3]. These stages are based on the assumptions that the viral entry by SARS-CoV2 will be the same as SARS-CoV, as we do not know if there is an alternative receptor for SARA- CoV [3].

Stage 1

Stage 1, also known as the asymptomatic state, consists of the initial one to two days on infection. During this stage, it is likely that the inhaled virus binds to epithelial cells that are found in the nasal cavity [6]. This is where it begins to start replicating. ACE2 is known to be the main receptor for both SARS-CoV2 and SARS-CoV [7]. Based on in vitro experiments, it is believed that the ciliated cells are the primary cells infected in the conducting airways [8]. However, other experimental data does not support this hypothesis as single-cell RNA indicated low levels of ACE3 expression in the conducting

airway cells, along with no cell type preference8. During this stage, there is a very limited innate immune response, and only local propagation of the virus [1].

A nasal swab may be used to detect the virus at this stage and although patients may not be experiencing many symptoms, these patients remain infectious [1]. Nasal swabs are believed to be more sensitive than throat swabs when it comes to detecting the virus [1]. The RT-PCR value for the viral RNA can be useful in determining the viral load, the infectivity and the clinical course [1]. This value could possibly allow super spreaders to be detected, helping to reduce the spread. However, in order to use RT-PCR cycle values, the sample collection must be standardized.

Stage 2

The next stage of the virus consists of the upper airway and conducting airway response. The virus now begins to propagate and migrate down the respiratory tract, including the conducting airways, which then triggers a more innate immune response [1]. A nasal swab or sputum at this stage would yield the virus along with early markers of the innate immune response [1]. By examining the level of CXCL 10, or possibly other innate response cytokines, one may be able to predict the subsequent clinical course [9]. CXCL 10 is an interferon responsive gene, known to be useful as a disease marker in SARS and influenza [10]. The viral defected epithelial cells are a major source of beta and lambda interferons [11].

By examining the host innate immune response, it may be possible to improve predictions on the subsequent course of the disease [1]. For approximately 80% of the infected patients, the disease will be restricted to the upper and conducting airways, while presenting mild symptoms [12]. These individuals do not need aggressive monitoring and may be monitored at home with conservative symptomatic therapy.

Stage 3

Unfortunately, approximately 20% of the infected patients will go past stage 2 and enter stage 3 of the disease [12]. These infected patients will develop pulmonary infiltrates and some may develop a very serious form of the disease [1]. Currently, the estimates of the fatality rate are about 2% but this varies according to the age of the patient [12]. These estimates may become better defined once the prevalence of mild and asymptomatic cases is better understood.

During this stage, the virus will now reach the gas exchange units of the lung and will begin to infect the alveolar type II cells [13] (Figure 2). These infected alveolar units are likely to be peripheral and subpleural [14]. This is a similarity between SARS-CoV and influenza, as they both preferentially infect type II cells rather than type I cells [15].

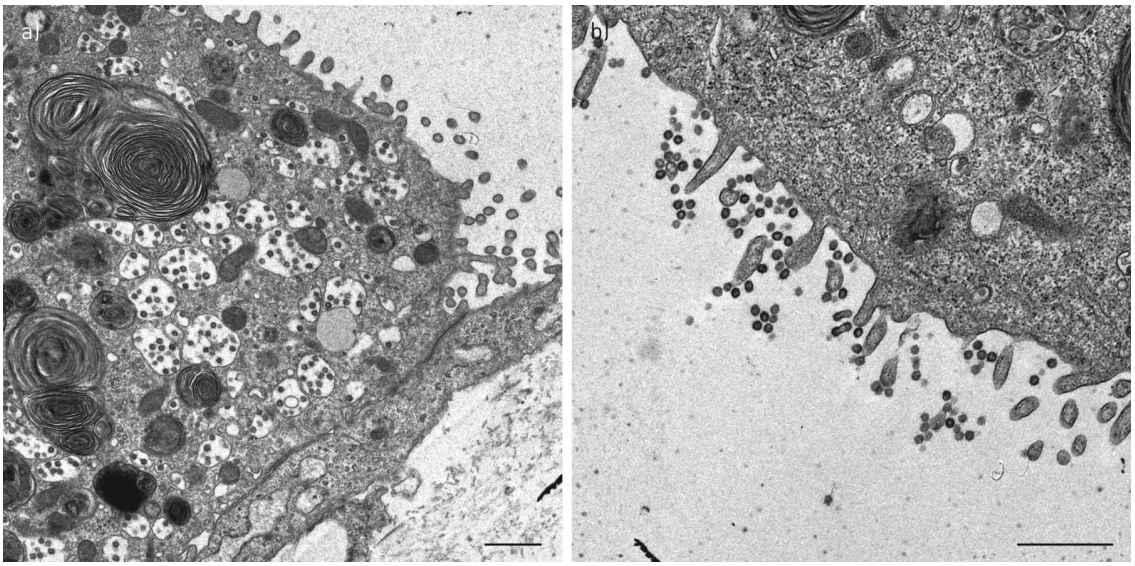

Figure 2: Human Alveolar Type II Cells infected with SARS-CoV [10].

As the virus propagates within the type II cells, large numbers of viral particles are being released, causing the cells to undergo apoptosis and die [10]. This results in a self-replicating pulmonary toxin, as the viral particles from the infected type II cells infect the adjacent cells [1]. Due to this rapid spread of viral particles, large areas of the lungs lose most of their type II cells, triggering the secondary pathway for epithelial regeneration [1].

Type II cells are of high importance, as they are typically the precursor cell for type I cells [16]. The pathological result of COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells [17]. The abnormal wound healing may result in scarring and fibrosis [18]. Recovery from these results may need a very vigorous innate and acquired immune response along with epithelial regeneration.

At this stage, it may seem useful to administrate epithelial growth actors such as KFG, but this may be detrimental due to increased viral load by producing more ACE2 expressing cells, as seen with influenza [19]. The elderly are at a higher risk due to their diminished immune response and reduced capacity to repair the damaged epithelium [1]. The elderly are particularly at risk due to their reduced mucociliary clearance, allowing the virus to easily spread to the gas exchange units of the lungs [20].

Figure 2 shows human alveolar type II cells were isolated, cultured in vitro and then infected with SARS-CoV10. The viral particles are seen in the double membrane vesicles in the type II cells. They can be seen along the apical microvilli [10].

TRANSMISSION

It is suggested that there is likely a zoonotic origin of the COVID-19 as it is believed to have originated in the wet animal market in Wuhan City [3]. There were a large number of infected people that were exposed to this market. The search for a reservoir host or intermediate carriers are ongoing, but this would help to explain how the infection spread to humans. There have been two species of snakes that are being investigated as possible reservoirs of the virus [3]. However, the experimental results have been inconclusive, and consistently display mammals and birds as coronavirus reservoirs [21].

It is likely that mammals are the most likely link between COVID-19 and humans as suggested using genomic sequence analysis [22]. It has also been observed that person-to-person transmission is the likely route utilized by COVID-19, which is evident in individuals and families who did not visit the wet animal market in Wuhan City [3]. Transmission between individuals occurs through direct contact or through droplets that are spread by an infected individual through coughing and sneezing [23]. A study was conducted on pregnant women in order to determine whether there is transmission from mother to child, and it showed that infected women in their third trimester did not transmit the virus to their children [24]. However, all these women had a cesarean section performed, meaning further studies on pregnant women that include vaginal birth are required [14].

PATHOGENESIS

There have been an increasing number of infected individuals and fatalities, particularly in the epidemic region of China [3]. When patients infected with COVID-19 were examined, it was discovered that they possess higher leukocyte numbers, abnormal respiratory findings and an increased level of plasma pro-inflammatory cytokines [3]. Many individuals infected with COVID-19 presented a cough, coarse breathing sounds from both lungs, a persistent fever and a body temperature averaging at 39.0^0C [3]. The COVID-19 infection was confirmed using real-time polymerase chain reaction [25]. The patients also showed leucopenia, having leukocyte counts of 2.91 x 10^9 cells/L, of which 70.0% were neutrophils [3].

To add on to that, the normal range of blood C-reactive proteins is 0-10 mg/L but infected individuals had an average value of 16.16 mg/L [3]. In these patients, high erythrocyte sedimentation rate and D-dimer was also exhibited [25]. Additionally, it was discovered that infected patients had higher blood levels of cytokines and chemokines, which included IL1-β, IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFNγ, IP10, MCP1, MIP1α, MIP1β, PDGFB, TNFα, and VEGFA [26]. Some of the infected patients had a more severe case, requiring the need of an intensive care unit, and these patients exhibited high levels of proinflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα [26].

These proinflammatory cytokines are believed to promote disease severity. The main findings in terms of pathogenesis of COVID-19 infection as a respiratory system targeting virus include RNAaemia, acute cardiac injury, ground-glass opacities and severe pneumonia [26].

PHYLOGENETIC ANALYSIS

COVID-19 is classified as a β CoV of group 2B by the World Health Organisation (WHO) [27]. Ten genomic sequences of COVID-19 were taken from nine patients and this exhibited a 99.98% [22] sequence identity. Another similar experiment using five patients demonstrated a 99.8-99.9% [28] nucleotide identity in the isolates. This study also revealed a new beta-CoV strain. By analyzing the genetic sequence of COVID-19 it was discovered that it showed more than an 80% similarity to SARS-CoV and 50% to MERS-CoV, which both originate in bats [28]. Using this evidence, it is clear that COVID-19 belongs to the genus betacoronavirus, which is the same genus as SARS-CoV, and infects humans, bats and wild animals [39].

The COVID-19 is classified under the orthocoronavirinae subfamily, which consists of seven members of the coronavirus family that have the ability to infect humans [39]. This virus forms a clade within the subgenus sarbecovirus. Although COVID-19 is similar to SARS-CoV, there are significant differences that permits it to be considered a new betacoronavirus that infects humans [3]. Along with its similarity to SARS-CoV and MERS-CoV, there is more evidence that supports the fact that COVID-19 is of bat origin. This includes the high degree of homology of the ACE2 receptors found in various animal species, making it a possibility that these animal species may act as possible intermediate hosts [6].

Continuing on, this virus has a single intact open reading frame on gene 8, which is a strong indicator of bat-origin CoVs [6]. The amino acid sequence of the receptor-binding domain is similar to that of SARS-CoV, which indicates that these two viruses may use the same receptor [28].

POSSIBLE TREATMENTS

As mentioned earlier, COVID-19 spreads person-to-person, which led to the isolation of infected patients. These isolated patients were administered a variety of treatments but there are no specific antiviral drugs or vaccines that have proven successful at the moment [3]. The current option is to utilize broad-spectrum antiviral drugs, such as Nucleoside analogues and HIV-protease inhibitors which work to attenuate the viral infection until a better treatment option is available [3].

A study including 75 patients included the administration of existing antiviral drugs. This included twice a day oral administration of 75 mg oseltamivir, 500 mg lopinavir, 500 mg ritonavir and the intravenous administration of 0.25 g ganciclovir for 3-14 days [31]. Another study showed that broad-spectrum antiviral remdesivir and chloroquine showed a significant improvement in infected patients in vitro [3]. These antiviral compounds have been previously used in human patients, allowing them to be considered to be used to treat COVID-19 [32].

There are other compounds that are being developed for the treatment of COVID-19 infection, which includes EIDD-2801, a compound that has shown promising results against seasonal and pandemic influenza virus infections [33]. As more time is needed until specific therapeutics become available for the treatment of COVID-19, it is important to consider more broad-spectrum antivirals. Some of these broad-spectrum antivirals include Lopinavir/Ritonavir, Neuraminidase inhibitors, peptide (EK1), RNA synthesis inhibitors [3]. However, it is clear that there is more research required urgently needed to identify drugs for treatment COVID-19.

In order to do this, there is an urgent need to create an animal model to replicate this disease, allowing the development of pre- and post-exposure prophylaxis. There is ongoing research, with several groups of scientists working to develop a nonhuman primate model, which would allow them to study the COVID-19 infection and test potential vaccines while better understanding the virus-host interactions [3].

FUTURE IDEAS

As there is no specific antiviral drug or vaccine for COVID-19, other extensive measures are required. This includes extreme measures to reduce the person-to-person transmission of COVID-19, which is absolutely essential to

control the current outbreak. These efforts to reduce transmission would be especially applied to susceptible populations, such as children, health care providers, and elderly people. It has been observed that the early death cases of the infection occurred primarily in elderly people [34]. This may be due to the fact that the older individuals have a weaker immune system, which permits faster progression of the virus [1].

In order to prevent the spread of the virus, public services should provide decontaminating reagents for cleaning hands in a routine manner. In addition to that, fecal and urine samples may potentially drive as an alternative route for transmission, so special attention should be applied when dealing with these objects along with other wet and contaminated objects [34]. Many countries have implemented various control measures, including travel screenings and mandatory 14-day isolation in order to control further spread of the virus [23].

The virus must be studied further, including any epidemiological changes. This includes studying new potential routes of transmission, adaptation, evolution and virus spread between humans and possible animals and reservoirs. There are still many questions that need to be answered, including who to test and how many tests need to be administered. There is also further research required in numerous cases, such as the fact that there have been very few pediatric cases, which may be due to lack of testing or a true lack of infection. By asking more questions and working to answer them, this will provide a framework to answer more specific questions, allowing more extensive public health measures to be implemented.

CONCLUSION

The current COVID-19 pandemic is a live issue that is affecting people all over the world. The number of death tolls continues to rise and many countries are being forced to go into lockdown and practice social distancing. It has changed the way the world works, with stricter regulations to prevent further spread of the virus. Currently, the lack of targeted therapies continues to be a significant problem, but broad-spectrum antiviral drugs are currently being administered [35]. There is a lot of ongoing research on various topics related to COVID-19, with the hope that we will be able to understand the virus better.

Epidemiological studies have shown that some populations such as the elderly are more susceptible and require special attention while children tend to have milder symptoms [35].

Genetic analysis has allowed the classification of the virus along with finding similarities between COVID-19 and previous viruses [1]. By using information gathered from previous viruses, the three clinical stages of COVID-19 have been established, which allows a better understanding of how the virus enters the body and progresses.

The symptoms and likelihood of death can range based on numerous factors, such as the strength of the immune system and the age. Various experiments have demonstrated the impact of the virus on the body, such as the changes observed in alveolar type II cells [10]. Its transmission method is quite clear but it may be possible for it to be transmitted in other ways, such as through fecal matter. It is not clear whether there is an animal reservoir and if it is truly from a bat origin, but further research will confirm these results [3]. Finding an animal model would facilitate the vaccine creation process, as this animal model could be used to better understand the way the virus interacts with the host and would allow vaccines to be tested. Without a specific antiviral drug, the current focus is to reduce the spread of the virus while providing supportive care for infected individuals [2].

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