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Review

Histopathology and Pathogenesis of Coronavirus disease 2019 (COVID-19)

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ABSTRACT

A severe pandemic of CoronaVirus disease 2019 (COVID-19), according to World Health Organization (WHO), appeared in China in December 2019, and spread rapidly. The majority of the patients had mild symptoms and good prognosis after recovery; however some patients developed severe inflammatory reaction and passed away from multiple organ complications. The novel coronavirus, Severe Acute Respiratory Syndrome Corona Virus 2 (SARS-CoV-2) is a beta-coronavirus and is similar with the Severe Acute Respiratory Syndrome Corona Virus 1 (SARS-CoV-1) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV). SARS-CoV-2 and -1 have the same host receptor, the angiotensin-converting enzyme 2 (ACE2). The pathogenesis of SARS-CoV-2 infection in humans remains unclear. The immune response is essential to control and reduce SARS-CoV-1 and -2 infections, however, irregular and exaggerated immune responses may lead to the immunopathology of the disease and the lung lesions. This article presents the immunological features of SARS-CoV-2 infection and its potential pathogenesis based on the recent observations of the International literature.

1. INTRODUCTION

Coronavirus disease 2019 (COVID-19) consists an acute respiratory clinical syndrome caused by a novel coronavirus which emerged in Wuhan in December 2019. The novel coronavirus, Severe Acute Respiratory Syndrome CoronaVirus 2 (SARS-CoV-2) is a beta-coronavirus and is similar with the Severe Acute Respiratory Syndrome CoronaVirus (SARS-CoV-1) and the Middle East Respiratory Syndrome Coronavirus (MERS-CoV), which were responsible for respiratory infections characterized by poor prognosis over the last 20 years [1]. The disease has been labeled a pandemic by the World Health Organization (WHO) on March 2020 and to date, has dramatic global economic and health implications as spread rapidly worldwide [2]. Previous studies have shown that the pathogenesis of SARS-CoV and MERS-CoV are not yet fully elucidated and it is possible that viraland host factors are implicated in it as hosts factors are responsible for an exaggerated immune response which may result in damage to the lung tissue and functional disorder [3-5].

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In individuals who suffer from COVID-19, a clinical syndrome has been observed which is considered as a main mechanism that is able to lead to the breakdown of the lungs, cardiovascular system, kidneys and liver. That syndrome is known as Cytokine Release Syndrome (CRS), and has been observed in other pathological conditions that activate the immune system to an extensive level, such as various infections or treatments that are able to overactivate the immune system [6]. CRS is the leading cause of serious morbidity in patients infected with SARS-CoV and MERS-CoV. Elevated serum Interleukin (IL) -6 levels have been found in patients with SARS-CoV-1, with which SARS-CoV-2 is closely linked, and are associated with respiratory failure, Acute Respiratory Distress Syndrome (ARDS), and poor clinical outcome [7, 8]. It has been estimated that 20% of COVID-19 patients will have severe symptoms of pneumonia, leading to ARDS [9]. This complication is similar to the ARDS caused by the release of cytokines and the Haemophagocytic LymphoHistiocytosis Syndrome (HLHS) previously observed in patients with SARS-CoV and MERS-CoV as well as patients with B acute lymphoblastic leukemia receiving genetically modified autologous T-lymphocytes (CAR-T cells) [10].

2. STRUCTURE OF CORONAVIRUS

Coronaviruses (CoVs) consist of positive-sense single-stranded RN virus genomes with a varied size 26-32 kilobases, whereas its virion consisted of a nucleocapsid with genomic RNA and phosphorylated nucleocapsid protein (PNP), which is located inside phospholipid bilayers and covered by two different types of spike proteins. Those proteins are the hemagglutinin-esterase protein (HEP) that is present in some CoVs, and the spike glycoprotein (SGP) which exists in all CoVs. The membrane protein (MP), a transmembrane glycoprotein type III, and the envelope protein (EP) are located among the SGPs proteins in the virus envelope. The coronavirus subfamily is classified into 4 subtypes, according to genotypical and serological criteria, the α, β, γ, and δ coronaviruses, whereas the β-coronavirus can be further divided into 4 viral members, A-D [11]. They have been isolated 30 CoVs that can contaminate humans, mammals, birds, and other animals. α- and β-CoVs are responsible for human infections which in general are associated with upper respiratory tract infections, whereas in some cases may infect lower respiratory tract [9,11].

The current classification of CoVs recognizes 39 species in 27 subgenera, five genera and two subfamilies that belong to the family Coronaviridae, suborder Cornidovirineae, order Nidovirales and realm Riboviria. CoV's family classification and taxonomy were developed by the Corona-viridae Study Group (CSG), which is responsible for assessing the place of new viruses through their association to known viruses in established taxa, including placements relating to the species SARS-related coronavirus [12]. Alphacoronovirus includes HCoV-229E and HCoV-NL63 species, whereas Betacoronovirus includes HCoV-OC43, HCoV-HKU1, SARS-CoV and MERS-CoV species [13]. Four human coronaviruses are endemic in the human population, namely HCoV-229E, HCoV-OC43, HCoV-NL63, and HCoV-HKU1. The first two viruses have been found out since the 1960s, whereas the emergence of SARS-CoV in 2002 led to a wide search for novel virus and the identification of HCoV-NL63 and HCoV-HKU1 in 2004 and 2005, respectively [14,15].

3. CYTOKINE UP-REGULATION IN SARS-CORONAVIRUS INFECTIONS

As mentioned, CRS is the leading cause of serious morbidity in patients infected with SARSCoV and MERS-CoV infections, and elevated levels of Il-6 and other inflammatory cytokines and chemokines have been identified in patients with the mentioned infections [7,8]. An elevated level of serum C - reactive protein (CRP), an acute-phase protein whose expression depends on IL-6 which is released by macrophages and T cells, is also an indicator of severe CoV infection. IL-6 is a pro-inflammatory mediator as promotes inflammation and its signaling pathways include the classic cis- and Trans signaling pathway [16]. In cis pathway, IL-6 binds to the membrane-bound IL-6 receptor (mIL-6R) and forms a complex with the gp130 membranic glycoprotein, which is expressed in all cells, whereas the mIL-6R receptor expression is limited in the immune system cells. The downstream signalling pathway is mediated by the JAK/STAT3 family kinases, and its activation leads to various effects in the innate / non-adaptive and mainly in the adaptive immune system. The final results are that B, T- lymphocytes and neutrophils, macrophages and NK killers, can be implicated in CRS development [16]. In trans signalling pathway, IL-6 binds to its soluble receptor, IL-6R (sIL-6R), and forms a complex with gp 130, on all cells membrane surface. IL-6/sIL-6R/JAK-STAT3 signalling pathway is activated even in cells which do not normally express the mIL-6 receptor, such as endothelial cells and leads to a systematic "cytokine storm" which contains the Vascular Endothelial Growth Factor (VEGF), Monocyte Chemoattractant Protein-1 (MCP-1), IL-8, and additional IL-6 release, whereas leads to a reduced expression of E-cadherin in endothelial cells. Increased levels of VEGF in combination with decreased E-cadherin expression are responsible for an increased vascular permeability and "leakage", mechanisms that are implicated in the pathophysiology of hypotension and lung dysfunction in ARDS [17].

Based on the finding that lymphocytopenia is often observed in severe COVID-19 patients, the CRS caused by SARS-CoV-2 virus has to be mediated by leukocytes other than T cells, as it has been found in patients receiving CAR-T treatment. Therefore it is possible that lymphocytopenia is also associated with the clinical

severity of the disease [18] and suppose a differential diagnostic criterion for COVID-19 [19]. However, lymphocytopenia has also been associated with a poor prognosis in other viral infections such as in influenza A H1N1 pandemic in 2009 [20] and can not be considered as a specific biomarker for CoVid-19 poor prognosis. SARS-CoV-1 infects dendritic cells and monocytes, MERS-CoV infects monocytes and T-lymphocytes through the receptor of dipeptidyl peptidase 4 (DPP4) [21, 22], whereas recent studies suggest that SARS-CoV-2 also infects dendritic cells. Dendritic cells dysfunction leads to abnormal T-lymphocytes activation which in turn may lead to their reduction and apoptosis, conditions that may contribute to the immunopathology of COVID-19 [21, 23]. Infection of monocytes, macrophages, dendritic and T-lymphocytes by SARS-CoV-2 leads to their activation and release of IL-6, CRP and other inflammatory cytokines and chemokines. IL-6 also suppresses.

4. HISTOPATHOLOGY OF LUNG LESIONS

The lung lesions of SARS patients are characterized by histopathological findings such as non-specific inflammatory responses with edema and inflammatory cell infiltration, severe alveolar epithelial cells exfoliation, alveolar septal swelling, alveolar septa damage, and alveolar space infiltration in an organized manner. SARS-CoV infection can cause pathological changes, degeneration, infiltration, and hyperplasia [11]. In a recent study by Tian et al. [24] which presented two cases treated by lobectomy due to lung adenocarcinoma, were subsequently diagnosed with COVID-19. Histopathological examination indicated that, in addition to adenocarcinoma, the lungs of both patients showed edema, protein release, lung cells focal reactive hyperplasia, and local infiltration by inflammatory cellular components. In addition, none of the patient showed symptoms of pneumonia during the surgical procedure and, therefore, the observed findings demonstrate early stages of the pathologic anatomical picture of the lung during the development of COVID-19 pneumonia. As already has been referred the pathogenesis of SARS and MERS are not yet fully elucidated, and it seems that viral and host factors play a principal role in SARS-CoV and MERS- CoV infections.

5. POSSIBLE PATHOGENESIS OF CORONAVIRUS DISEASE

According to clinical studies that are based on the International literature reasonable hypotheses has been suggested regarding the pathogenesis of SARS-CoV-2 infection. SARS-CoV-2 might go through the nasal and larynx mucosa membranes, and finally through the upper respiratory tract enters the lungs and from the lungs enter the peripheral blood circulation leading to viremia [25]. SARS-CoV-2 and SARS-CoV use the same receptor ACE2 (angiotensin-converting enzyme) to enter the cells. ACE2 receptor is widely expressed in lung and cardiovascular cells and in mono-cytes and macrophages, kidney and gastrointestinal tract [26, 27]. Then the virus would attack the targeting organs that express ACE2. SARS-CoV-2 binds via the ACE2 receptor, which is located on the surface of Alveolar Type II

Cells (AT II), and have a crucial role in innate immunity as they express on their surface specific receptors for antigens of viruses and bacteria, Toll-like receptors (TLRs) and induce the production of inflammatory cytokines, chemokines and molecules that attract other immune cells, neutrophils and macrophages in response to the invasion of pathogenic viruses and bacteria [28, 29]. The mentioned hypothesis is supported by the finding that the SARS-CoV-2 has been detected in fecal samples [25], finding that shows its transmission from the lungs to blood circulation and to intestine system. Wang et al. found that the median time from symptom start to ARDS development was about 8 days [30]. Therefore it is possible that the virus begins a second attack, leading to the patient's condition to deteriorate around 7-14 days after onset. During that period, the number of leukocytes in peripheral blood in the early stage of the disease was normal or slightly low [25], whereas lymphopenia was a common finding [30].Based on the observation that in cases of severe disease, lymphocytes were significantly reduced [30], it is possible that B-lymphocytes reduction may occur early in the disease, which may affect antibody production in the patient and lymphocytes in patients with COVID-19 might gradually decrease during the disease progression. However, the mechanism of that significant lymphocyte reduction in severe SARS-CoV-2 infection remains unclear [31]. Moreover, the inflammatory factors associated with diseases mainly containing IL-6 were significantly increased, which also contributed to the deterioration of the disease around 7-14 days after onset [32].

Lin et al. divided the clinical phase into three stages, the viremia stage, the acute stage which is characterized by development of pneumonia and the recovery stage. Patients in the acute stage will be able to enter the recovery stage in case their immune system is effective and have no other disease, such as hypertension and diabetes mellitus. In case of older patients or ineffective immune system with other systematic disease may result in negative prognosis [31]. SARS-CoV is diffused in AT II cells, release a large amount of viral particles, the cells undergo apoptosis and die. This condition may result in infection of AT II cells in adjacent locations [33]. Mason [34] supported that lung areas it is possible to lose a large number of AT II cells, and secondary pathway ways for epithelial regeneration will be triggered. Normally, type II cells are the precursor cells for type I cells. Those suggestions have been observed in mice model of influenza pneumonia [35, 36].

The pathologic outcome of SARS and COVID-19 diseases is a diffuse alveolar damage with fibrin rich hyaline

membranes and a limited number of multinucleated giant cells [37, 38]. The abnormal wound healing may lead to more severe fibrosis and scarring than other types of ARDS. The stage of recovery it is possible to demand an innate and acquired immune response and epithelial regeneration [34]. Jin et al. referred that COVID-19 pathogenesis could be attributed to cytotoxic and immunemediated mechanisms [39], whereas a previous study mentioned that viral entry and subsequent cell damage could be attributed to the antibody-dependent enhancement (ADE), which consists a cascade of procedures by which viruses may infect susceptible cells through interaction between viruses particles with antibodies or complement proteins, or Fc- or other receptors, resulting in the amplification of their proliferation [40] It is possible that CD209L is an alternative receptor for SARS-CoV-2 cell entry and maybe is implicated in COVID-19 pathogenesis [41].

In conclusion, up to now pathogenesis of COVID-19 is still unclear. Further studies are needed to focus on possible alternate receptors for viral entry and the innate immune response of differentiated lung cells in an effort to eliminate cytokine deregulation and the development of specific anti-viral drugs.

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