Respir Case Rep 2023;12(3):127-134 DOI: 10.5505/respircase.2023.98752

RESPIRATORY CASE REPORTS

COVID-19 Cytokine Storm and the Mechanisms of Immune Injury

COVID-19 Sitokin Fırtınası ve İmmün Hasar Mekanizmaları

Ali İnal, Dilaver Taş

Abstract

The first cases of COVID-19 were identified in China in 2019, and the disease subsequently spread rapidly around the world, leading it to be declared a pandemic. The disease affects the lungs through the upper and lower respiratory tracts, and with the development of pneumonia, a clinical picture leading to respiratory failure referred to as cytokine storm occurs as a result of excessive cytokine production associated with an excessive inflammatory immune response. The increase in inflammatory markers is related to acute respiratory distress syndrome, disseminated intravascular coagulation and hypercoagulation. We present here an explanation of cytokine storm and the associated immune damage mechanisms.

Keywords: *Cytokine storm, COVID-19, immunopathogenesis.*

Öz

COVID-19 olguları ilk olarak 2019 yılında Çin'de ortaya çıkmış ve daha sonra hızlı bir şekilde yayılarak dünyada pandemiye yol açmıştır. Hastalık üst solunum yollarını tutmakta ve daha sonra alt solunum yollarına yayılarak akciğerleri etkilemektedir. Pnömoni gelişimi ile birlikte aşırı inflamatuar immün yanıt gelişimine bağlı aşırı sitokin üretimi sonucu sitokin fırtınası olarak adlandırılan solunum yetmezliğine kadar giden klinik tablo ortaya çıkmaktadır. İnflamatuar göstergelerdeki bu artış; akut solunum sıkıntısı sendromu (ARDS), dissemine intravasküler koagülasyon (DİK) ve hiperkoagülasyonla ilişkilidir. Bu makalede sitokin fırtınası ve COVID-19'da immün hasar mekanizmaları açıklanmıştır.

Anahtar Kelimeler: *Sitokin fırtınası, COVID-19, immünopatogenez.*

Başkent University İstanbul Health Practice and Research Center, İstanbul, Türkiye

Başkent Üniversitesi İstanbul Sağlık Uygulama ve Araştırma Merkezi, İstanbul

Submitted (Başvuru tarihi): 16.03.2023 ***Accepted (Kabul tarihi):*** 30.05.2023

Correspondence (İletişim): Dilaver Taş, Başkent University Istanbul Health Practice and Research Center, İstanbul, Türkiye

e-mail: dilavertas@gmail.com

The first case of coronavirus disease 2019 (COVID-19) was reported in the city of Wuhan, China [1], and the causative virus was identified shortly after, when an increasing number of patients presented with similar symptoms of respiratory tract infection. The causative viral agent was an RNA virus that was named subsequently "severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2)", the primary transmission route of which was identified as direct or indirect contact with the respiratory droplets of asymptomatic carriers or patients, and the rapid transmission of the virus from one person to another was the primary obstacle to disease control (1). To date there have been 681,591,554 reported cases of the disease and 6,812,126 deaths (2). The coronavirus has four different structural proteins that play an important role in its lifecycle: the S protein, forming the spikes on the surface of the virus, which are responsible for binding the virus to the host cell membrane (3); the M protein, which is involved in the establishment of the viral shape, and also plays a role in the formation of viral particles and budding from the cell membrane through a process known as scission (4); the E protein, which is involved in the assembly and budding of the virion, and plays a role in viral pathogenesis; and the N protein of the virus, which has multiple functions, and is capable of binding to viral RNA through two binding domains. The N protein interacts with viral nonstructural protein 3 (nsp3) to package the genome and promote virion assembly, and maintains viral integrity against intracellular defense systems (4,5). SARS-CoV-2 has demonstrated an ability to enter cells through different mechanisms, but mainly by direct membrane fusion, with the angiotensin-converting enzyme 2 (ACE2) receptors being the main binding site and playing a crucial role in the entry of the virus into the cell and viral replication (6). The S protein of SARS-CoV-2 binds to ACE2 receptors and fuses with the plasma membrane and is proteolytically processed after binding to the ACE2 receptor, which is an important stage in the lifecycle of the virion (5). Our understanding of how SARS-CoV-2 enters cells remains open to further refinement, although it is known to gain entry through the formation of viral inclusion bodies upon contact with cellular surface elements.

In addition to membrane fusion, both clathrin-mediated and clathrin-independent endocytosis mechanisms have been reported. Clathrin is a basic protein that plays a role in the assembly of extracellular vesicles into a specific shape. Once the single-stranded positive-sense RNA genome gains entry to the cell, it is released into the cytoplasm, and as a result, the transcription and translation of viral products take place (7). ACE2 receptors are expressed in various tissues, including alveolar cells, bronchial epithelial cells, and the liver, neurons, glia, pancreas, stomach, bowel, heart and kidneys (8). The internalization and cleavage of ACE2 during the entry of the virus into the host cell affects also the renin-angiotensin system (RAS) and results in an increased serum level of angiotensin-2. ACE2 receptors are also expressed in endothelial cells, and viral inclusion bodies can be observed in the endothelial cells upon contact with the virus. The endothelitis, apoptosis and imbalance in RAS resulting from endothelial cell infection have been linked to a variety of conditions, such as ischemia, edema and hypercoagulability (9,10). Antibody-dependent enhancement (ADE) is another potential route for the entry of SARS-CoV-2 into cells. In the presence of anti-S antibodies, the virus enters the host cells that harbor Fc-γ-2 (CD32) receptors on their surfaces in the form of an antibody-virus complex, and thus exerts cytopathic effects. It is thought that the entry of SARS-CoV2 into monocytes and macrophages through ADE could play a role in cytokine and chemokine release and apoptosis (11,12).

The body's natural immune response elements are the first-line defense in the recognition and clearance of viral infectious agents. The leading factor in the activation of a natural immune response is the recognition of the pathogen-associated molecular pattern (PAMP) of the virus in the form of lipid, protein and nucleic acid by toll-like receptors (TLRs). It has been suggested that the S protein can be recognized from TLR4, that ssRNA can be recognized from TLR7/8, and that the dsRNA that forms during replication can be recognized from TLR3. TLR3 and TLR4 induce interferon regulatory factor 3 (IRF3) over the toll-interleukin1 receptor (TRIF) domain-containing adaptor-inducing interferon-β and the TRIF-related adaptor molecule (TRAM), leading IRF3 to accumulate in the nucleus and initiate interferon (INF) synthesis. Upon recognizing a foreign or a disrupted molecule, the cell instructs the neighboring cells to correct the problem, and these pathways are crucial elements in the innate immune response to viruses. Coronaviruses are capable of concealing pathogen-associated molecular patterns (PAMPs) and can also prevent intracellular receptors from recognizing them (13). They have also developed various mechanisms through which they can evade recognition by host cells, such as by concealing themselves within double-layered endosomal structures and disrupting the timing and magnitude of the host's interferon (IFN) response to infection. Despite being vulnerable to the immune responses mediated by interferon (IFN), SARS-CoV and other coronaviruses have evolved multiple mechanisms that make them resistant to type-I IFN-mediated responses, allowing the virus to evade the host's immune defenses and cause significant damage to the infected patient (14,15). Studies investigating the role played by T and B lymphocytes in mice infected with SARS-CoV have revealed that T cells play a crucial role in clearing the virus and supporting the

host's immune defense, and that the weak virus-specific T cell response is linked to the development of severe disease. In cases of SARS-CoV infection, approximately 80% of the cells that infiltrate the lungs are CD8 cytotoxic T cells (16). The importance of a robust T cell response for the successful clearance of viral infections is well understood, and this is the case also in SARS-CoV-2 infections. The development of lymphopenia in COVID-19 patients has been well-documented and is of prognostic significance (17). The CD4/CD8 cell ratio appears to remain stable in patients with COVID-19, with no notable changes identified in CD4 marker expressions to date, while an upregulation in the intensity of CD8 on the surface of lymphocytes has been observed. Given the crucial role of the CD8 protein in mediating cytotoxic activity, it has been suggested that cytotoxic T lymphocytes (CTLs) increase CD8 expression to facilitate effective antiviral activity (18). In humans, memory T cells specific to SARS-CoV have been detected in the blood up to 6 months after infection, while conversely, there would appear to be a significant deficiency in the specific memory B cell response. During the course of the disease, patients exhibit decreases in total lymphocyte count, CD4-positive and CD8-positive T cells (while the CD4/CD8 ratio is preserved), as well as B-lymphocytes and natural killer cells in the peripheral blood (19,20). Furthermore, memory helper T cell and T-regulator cell counts are remarkably low, and patients with more severe infections have been found to exhibit lower total lymphocyte, CD4-positive and CD8-positive T-cell, and B-lymphocyte counts than those with milder forms of the disease (6,20,21). Peripheral blood analyses of patients with severe forms of the disease have revealed increased expressions of HLA DR in both CD4- and CD8-positive cells, and increases in CD4+, CCR4+, CCR6+ and Th17 cell counts have also been observed (22). Notably, autopsy studies have revealed the destruction of secondary lymphoid organs over the course of the disease, while examinations of lung specimens have revealed prominent infiltrations of CD4-positive cells (23).

Patients with severe COVID-19 infections who require admission to the intensive care unit (ICU) tend to have increased erythrocyte sedimentation rates (ESR), and C-reactive protein (CRP), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and IL-1β, IL-8 and IL-2R levels, and such observed increases in inflammatory markers have been linked to the development of acute respiratory distress syndrome (ARDS), disseminated intravascular coagulation (DIC) and hypercoagulability. Another study reported significant differences in the IL-2, IL-7, IL-10, granulocyte colony-stimulating factor (G-CSF), inducible protein 10 (IP10), monocyte chemoattractant protein-1 (MCP-1), macrophage inflammatory protein 1α (MIP-1α) and TNF-α levels of patients requiring admission to the ICU when compared to those who do not require such care. Severe COVID-19 has been linked to increased inflammatory cytokine response. ARDS is induced by an exaggerated inflammatory response rather than the viral load (24). There are two primary reasons for the development of immune regulation disorders: one is the overproduction of proinflammatory cytokines by monocytes, and the other is related to the acquired immune system disorder that arises due to the depletion of CD4-positive lymphocytes. IL-6 is released in excessive amounts upon the hyperactivation of monocytes, leading to a decrease in the expression of HLA-DR on the antigen-presenting cells, especially in CD14-positive monocytes, and reduced IFN-γ (interferon-γ) secretion by CD4-positive cells. The inhibition of the IFN pathway and excessive viral load, together with the decreased viral response of the host and the persistent proinflammatory response can lead to deterioration in the patient as a result of excessive inflammation. IFN response can thus be understood to play a vital role in limiting SARS-CoV-2 infection and in activating innate and acquired immune responses. In SARS-CoV-2 infections, these responses are often delayed and inadequate, which is believed to be associated with the development of cytokine storms. While the exact mechanism by which viruses enter cells is not yet fully understood, studies have suggested that both previous coronaviruses and the novel SARS-CoV-2 induce apoptosis by triggering an overproduction of such proinflammatory mediators as IL-6, GM-CSF, IL-1s and TNF, as well as activating the NLRP3 inflammasome in monocytes and macrophages, which can, in turn, lead to cytokine storm, referred to also as cytokine release syndrome (25). It has been suggested that elevated serum ferritin, IL-6, IL-1β, IFN-γ, IP-10 and MCP-1 levels play a role in the pathogenesis of severe COVID-19 (26,27), and point to the activation of Th1 lymphocytes, which are involved in the differentiation of mature B lymphocytes into plasma cells, the transformation of growth factor-β (TGF-β)-mediated differentiation of naive CD4-positive T lymphocytes into TH17 lymphocytes, and the initiation of the production of acute phase proteins such as CRP, fibrinogen, serum amyloid A and hepcidin. IL-6 initiates the maturation of megakaryocytes into platelets and the activation of hematopoietic stem cells within the bone marrow (28,29), and increased serum IL-6 levels have been linked to respiratory failure, ARDS and unfavorable clinical outcomes. It has been noted that COVID-19 patients with high IP-10, MCP-1 and TNFα levels often require monitoring in the ICU, while those with lower levels of these markers tend to have a milder disease course that does not require ICU admission. Unlike SARS caused by SARS-CoV, there is an increased immune-focused release of IL-4 and IL-10 from the TH2 lymphocyte in COVID-19 caused by SARS-CoV-2 that suppresses inflammation. The excessive release of

pro-inflammatory cytokines (IFN-α, IFN-γ, IL-1β, IL-6, IL-12, IL-18, IL-33, TNF-α and TGF-β) and chemokines (CXCL10, CXCL8, CXCL9, CCL2, CCL3 and CCL5) is associated with accelerated and persistent abnormal systemic inflammatory response. The cytokine storm observed in severe COVID-19 patients is a significant risk factor for increased mortality, multi-organ failure, acute respiratory distress syndrome (ARDS) and disseminated intravascular coagulation (DIC). In particular, IL-6, which is released from macrophages, has been reported to contribute to the development of macrophage activation syndrome (MAS) (28). Studies have reported that plasma levels of IL-6, which is considered a critical cytokine for the development of MAS, are increased in both mild and severe COVID-19 cases, while significantly higher IL-6 levels have been observed in those with a severe form of the disease. IL-6 is a pleiotropic cytokine that is produced by a variety of immune cells, mesenchymal cells, endothelial cells and fibroblasts in response to infections and tissue injury. Monocytes, macrophages and dendritic cells become activated upon infection with beta coronavirus, and this leads to a release of IL-6 and other inflammatory cytokines that can trigger a cytokine storm. IL-6 is capable of signaling through various pathways, however, in the classic (cis) signaling pathway, IL-6 binds to the IL-6 receptor expressed on the surface of lymphocytes that form a complex with glycoprotein 130 (gp130), activating the Janus kinase (JAK) signal transducer and the activator of the transcription (JAK/STAT) pathway. The secondary message affects the B and T cells, suppressing the development of T-regulator cells by increasing the differentiation of T helper 17 (Th17), T follicular helper (Tfh) and CD8-positive cytotoxic T cells, as well as activated B cells. Such decreases in T-regulator cells complicate the control of immune response, and IL-6 may exert different effects on the acquired and innate immune systems via this pathway. In the trans-signaling pathway, IL-6 binds to soluble IL-6 receptors and triggers the JAK/STAT pathway over the gp130 complex in cells that do not express IL-6R (mIL-6R) on their membranes, such as endothelial cells. This pathway affects endothelial cells in the blood vessels with vascular endothelial growth factor (VEGF), increasing the release of MCP-1, IL-8 and IL-6, and decreasing E-cadherin synthesis, leading to increased vascular permeability and vessel leakage. These effects contribute to the development of hypotension and ARDS, and lead to a further deterioration in the patient's clinical condition. IL-6 has also direct effects on the synthesis function of the liver, increasing the release of CRP, serum amyloid A, hepcidin, fibrinogen, thyroid peroxidase (TPO), C3 and ferritin from the organ. Both the classic (cis signaling) and trans-signaling pathways contribute to the development of cytokine storm, leading to pulmonary dysfunction and the emergence of SARS symptoms, while cytokine storm leads also to the depletion of T lymphocytes (CD3, CD4, CD8), apoptosis and the development of lymphopenia. Studies examining the pulmonary infiltrates of COVID-19 patients who develop ARDS have suggested a link between extensive lung damage and increased IL-6 levels, and a decrease in CD4, CD8, natural killer (NK) and NKT counts in peripheral blood samples (30,31).

Innate lymphoid cells (ILCs) are effector cells that respond to environmental cytokines and regulate immune response, and that do not express the antigen receptors found on the surface of T and B cells. Tissue-resident ILCs are categorized as cytotoxic and non-cytotoxic, among which the cytotoxic cell group comprises conventional natural killer cells, whereas the non-cytotoxic cell group, the main function of which is cytokine release, is made up of three subgroups. Similar to T-helper cells, the ILC1 cell group is composed of IFN-γ-producing cells, the ILC2 cell group is composed of cells that produce IL-4, IL-5 and IL-13, and the ILC3 cell group is composed of those producing IL-17/IL-22 (32). There are limited data on the roles played by cytotoxic natural killer cells and ILCs in COVID-19, although it has been demonstrated that ILC1 and ILC3 express such ligands as CD26, CD147 and cyclophilins that interact with SARS-CoV-2. Studies of COVID-19 have produced different data on the number of natural killer cells in patients. While there are several studies reporting no significant difference in the number of NK cells in COVID-19 patients when compared to healthy controls, only a single study has reported a remarkable increase in NK cell counts, and the authors suggest that this may have triggered a cytokine storm (33-34). There are many other studies, however, that have reported low or significantly decreased NK cell counts in patients with severe SARS-CoV-2 (35,36), and the functional depletion of NK and cytotoxic CD8-positive T cells has been linked to severe SARS-CoV-2 infection. Although the production of CD107a, IFN-γ, IL-2, granzyme B and TNF-α was decreased in the depleted NL and CD8-positive T cells, an overexpression of CD94/NK group 2 member A (NKG2A), acting as an inhibitory receptor, was reported in these cells (20). HLA-E is an NKG2A ligand expressed by epithelial cells, and NKG2A is known to inhibit cytotoxicity and prevent the control of infection by binding to the non-classic HLA-E molecule (37).

The complement system is a component of the innate immune response that plays a critical role in host defense, although an uncontrolled and exaggerated response of the complement system can lead to acute lung injury. C5a activates phagocytic cells, stimulating cytokine release from the activated cells and can lead to a cytokine storm. C5a exerts its effects through C5aR in antigen-

presenting cells, which affects the proliferation and differentiation of CD4-positive T-helper cells and is also involved in the activation of cytotoxic CD8-positive T cells. Considering all these aspects, C5a can be said to contribute to the development of cytokine storm and ARDS by increasing the release of proinflammatory cytokines into both the innate and acquired immune systems, and it is believed that an excessive release of C5a may play a role in the development of severe respiratory failure, resulting in the release of such proinflammatory cytokines as IL-12, TNF-α and MIP-1α by inducing the mast cells, neutrophils, monocytes and macrophages. It has also been reported to induce the release of such cytokines as TNF-α, IL-1β, IL-6 and IL-8 by stimulating B and T cells (38,39).

The immune response mediated by cytotoxic CD8-positive T cells in COVID-19 neutralizes all cells infected by the virus, while CD4-positive T-helper cells help B cells initiate humoral responses. SARS-CoV-2 infects T lymphocytes through the binding of the spike protein (S1) to the CD147 ligands found on the surface of T lymphocytes. CD147 is expressed in a diverse range of tissues and cell types, and is involved in cell proliferation, apoptosis and tumor cell migration, metastasis and differentiation, especially under hypoxic conditions. The spike protein of SARS-CoV-2 has been reported to interact directly with CD26 in host cells (40). CD26 is a surface glycoprotein that contributes to T-cell activation and proliferation by interacting with the T cell receptor, and is expressed in high levels in CD4-positive and CD8-positive T cells, while displaying lower expression levels in dendritic and NK cells. The binding of the S protein of SARS-CoV-2 to the CD26 and CD147 molecules that play a role in T-cell activation suggests that the depletion of T cells by the infection can lead to cell death. It would seem plausible to suggest that the development of lymphopenia in patients with SARS, MERS (Middle East respiratory syndrome) and COVID-19 could be associated with the depletion of T cells (41,42). Following the infection of respiratory tract epithelial cells by SARS-CoV-2, viral peptides are presented to cytotoxic CD8-positive T cells via class I major histocompatibility complex (MHC) molecules. CD8-positive T cells become activated and begin to proliferate, developing virus-specific effector and memory T cells through clonal expansion. Cytotoxic CD8-positive T cells eliminate virus-infected cells through various cytotoxic mechanisms, including perforins and granzymes (43). CD8-positive T cells are of critical importance in mediating clearance following various acute viral infections in the lungs, while memory CD8-positive cells protect against secondary infections. There have been studies reporting, however, that total CD8 T and NK cell counts are diminished in COVID-19 due to lymphopenia, and cytotoxic lymphocytes are functionally depleted in SARS-CoV-2 infections in association with lymphopenia. The upregulation of NKG2A is believed to be responsible for the loss of NK and CD8-positive T-cell functionality, and it has been reported that NK and CD8-positive T-cell levels normalize in parallel with the downregulation of NKG2A in COVID-19 patients whose clinical status improves following treatment. These findings suggest that compromised antiviral response may contribute to the severity and pathogenesis of COVID-19. An immune response that is insufficient in suppressing viral replication and eliminating virus-infected cells can have systemic implications, including the development of clinically severe ARDS and disseminated intravascular coagulation, which can lead also to severe inflammatory response and may culminate in a cytokine storm (44).

Regulatory T cells (Tregs) play an important role in the suppression of excessive immune responses to pathogens, cancer cells and transplanted tissues, while also preventing the development, and controlling the progression of autoimmune and allergic diseases. The role of molecular mechanisms underlying the regulation of fork head box P3 (FOXP3) expressions and the antigen-specific response of Treg cells in COVID-19 remains ambiguous, and so further investigations are required to establish their clinical significance in this sense. On the other hand, a decrease in circulatory Treg cells (CD3+, CD4+, CD25+, CD127) has been observed aside from lymphopenia in COVID-19 patients (43-45). B and T lymphocytes are activated in response to SARS-CoV-2 infections, leading to the production of neutralizing antibodies. Initially, macrophages, acting as professional antigen-presenting cells, present the virus and its peptides to CD4-positive T helper cells via MHC class II molecules, while B cells can also become activated through the direct recognition of the SARS-CoV-2 nucleocapsid protein. The detection of primary virus-specific IgM antibodies is possible within the first week (4–8 days) of the onset of symptoms, and this initial IgM response is followed by the production of IgA and then IgG antibodies (10–18 days). The production of mucosal IgA antibodies plays a role in the prevention of re-infection with SARS-CoV-2, whereas IgA in the circulation may be effective in suppressing infection by contributing to the systemic neutralization of SARS-CoV-2 (46,47). The quality and extent of the IgG antibody response play a critical role in the neutralization of SARS-CoV-2. Given the limited time since the COVID-19 outbreak, the effective duration of the protective levels of virus-blocking antibodies is currently unknown. A study examining the data of previous SARS-CoV infections reported that the neutralizing IgG antibodies may be specific to the S protein of SARS-CoV-2, and that levels should be detectable in serum 2–3 weeks after infection (47). Neutralizing antibodies interact with various components of the immune system, including the complement cascade, phagocytes and NK cells. IgM antibodies are linked

mainly to complement activation and the release of pro-inflammatory cytokines, whereas IgG antibodies stimulate an immune response through FcR-expressing cells (48). A study examining the IgG and IgM antibodies that are generated to counter the SARS-CoV-2 proteins found an early and robust antibody response, characterized by high titers, to be associated with the development of severe disease, while a weak IgG response was found to be associated with higher viral clearance. These findings indicate an unforeseen relationship between robust antibody response and disease severity, and a relationship between weak antibody response and viral clearance (49). ACE2, which is suppressed and sheds to the environment during the entry of the virus into the cells, affects pulmonary permeability via RAS, leading to the development of pulmonary edema, and can play a role in immune dysfunction through the promotion of excessive T-cell activation. Anti-S-IgG can increase systemic inflammatory responses by stimulating a variety of cell types via the ADE phenomenon, leading to the development of viral sepsis and multiorgan failure. The effects of COVID-19 on vessels, however, is a component of the disease that has yet to be fully understood, although existing data suggest that COVID-19 may cause microangiopathy, independent of thrombosis, and is not limited to the pulmonary system. Immune dysfunction, systemic inflammatory response and RAS dysfunction can all contribute to the development of a cytokine storm, and COVID-19 can lead to death due to ARDS and respiratory failure unless cytokine storm, pulmonary edema and organ injuries can be well controlled (50). A hypercoagulable state has been demonstrated in many cases of severe pneumonia associated with SARS-CoV-2 infection, and the increased mortality associated with COVID-19 patients with coagulopathy suggests that the coagulation cascade may play a significant role in the pathogenesis of the disease (51). These observations are supported by clinical findings indicating that patients with D-dimer levels exceeding 3 μg/mL benefit from heparin therapy, and that anticoagulant therapies have been successful in reducing mortalities. A hypercoagulable state may have serious consequences, including cerebrovascular events such as stroke and cardiovascular events such as pulmonary thromboembolism, as well as miscarriage, arterial and venous thrombosis and osteonecrosis. Hypoxia resulting from respiratory failure can trigger a signaling pathway related to the hypoxia-inducible transcription factor (HIF) or may directly increase blood viscosity, while pulmonary hyperinflammation can cause elevated TPO levels, leading to a predisposition to thrombocytosis and thrombosis (52,53).

A cytokine storm can cause the overactivation of the coagulation cascade. Previous studies have suggested that such viral infections as hepatitis C virus, human immunodeficiency virus (HIV), cytomegalovirus (CMV), varicella-zoster virus, Epstein-Barr virus, adenovirus and parvovirus B have the potential to increase the production of antiphospholipid antibodies. Antiphospholipid syndrome stimulated by the virus has also attracted attention in COVID-19 patients, with studies conducted in this direction detecting anti-cardiolipin IgA, anti-β2-glycoprotein 1 IgA and IgG antibodies in the older patient group with such underlying comorbidities as hypertension and diabetes and a history of multiple cerebral infarctions, as well as findings consistent with antiphospholipid syndrome. That said, whether SARS-CoV-2 contributes significantly to the production of such antibodies requires further study (54). It has also been suggested that systemic and local increases in angiotensin 2 levels observed after the internalization and destruction of ACE2 upon the entry of the virus into the cell may facilitate the development of thrombosis (10). The activation of a coagulation cascade, triggered by the destruction of the endothelium, would appear to be one of the primary factors contributing to the development of a hypercoagulable state (9).

In conclusion, COVID-19 can stimulate the production of severe pathologies in many tissues, aside from the destruction it causes in the respiratory tract and can result in widespread systemic complications that may culminate in multiorgan failure. While SARS-CoV-2 infection can be asymptomatic, it can also lead to such serious conditions as ARDS, respiratory failure, MAS, DIC, widespread thromboembolism and even death. Although there are still several unknown factors related to the virus that require further research for elucidation, studies to date have done much to clarify the immunopathogenesis underlying the emergence of this severe disease in humans. The long-term consequences of the disease can be a point of particular interest in future studies.

CONFLICTS OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

Concept - A.İ., D.T.; Planning and Design - A.İ., D.T.; Supervision - A.İ., D.T.; Funding - A.İ., D.T.; Materials - D.T.; Data Collection and/or Processing - B.A.Ş., T.Ö.; Analysis and/or Interpretation - A.İ., D.T.; Literature Review - A.İ., D.T.; Writing - A.İ., D.T.; Critical Review - A.İ., D.T.

REFERENCES

1. Coronaviridae Study Group of the International Committee on Taxonomy of Viruses. The species Severe acute respiratory syndrome-related coronavirus: classifying 2019-nCoV and naming it SARS-CoV-2. Nat Microbiol 2020; 5:536-44. [CrossRef]

2. https://www.worldometers.info/coronavirus/ Erişim tarihi:13 Mart 2023
3. Beniac DR, Andonov A, Grudeski E, Booth TF. Architecture of the SARS coronavirus prefusion spike. Nat Struct Mol Biol 2006; 13:751-2. [CrossRef]
4. Belouzard S, Chu VC, Whittaker GR. Activation of the SARS coronavirus spike protein via sequential proteolytic cleavage at two distinct sites. Proc Natl Acad Sci U S A 2009; 106:5871-6. [CrossRef]
5. Nal B, Chan C, Kien F, Siu L, Tse J, Chu K, et al. Differential maturation and subcellular localization of severe acute respiratory syndrome coronavirus surface proteins S, M and E. J Gen Virol 2005; 86:1423-34. [CrossRef]
6. Montazersaheb S, Hosseiniyan Khatibi SM, Hejazi MS, Tarhriz V, Farjami A, Ghasemian Sorbeni F, et al. COVID-19 infection: an overview on cytokine storm and related interventions. Virol J 2022; 19:92. [CrossRef]
7. Li X, Geng M, Peng Y, Meng L, Lu S. Molecular immune pathogenesis and diagnosis of COVID-19. J Pharm Anal 2020; 10:102-8. [CrossRef]
8. Beyerstedt S, Casaro EB, Rangel EB. COVID-19: angiotensin-converting enzyme 2 (ACE-2) expression and tissue susceptibility to SARS-Cov-2 infection. Eur J Clin Microbiol Infect Dis 2021; 40:905-19. [CrossRef]
9. Varga Z, Flammer AJ, Steiger P, Haberecker M, Andermatt R, Zinkernagel AS, et al. Endothelial cell infection and endotheliitis in COVID-19. Lancet 2020; 395:1417-8. [CrossRef]
10. Magro C, Mulvey JJ, Berlin D, Nuovo G, Salvatore S, Harp J, et al. Complement associated microvascular injury and thrombosis in the pathogenesis of severe COVID-19 infection: a report of five cases. Transl Res 2020; 220:1-13. [CrossRef]
11. Yip MS, Leung HL, Li PH, Cheung CY, Dutry I, Li D, et al. Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS. Hong Kong Med J 2016; 22(3 Suppl 4):S25-31.
12. Wang SF, Tseng SP, Yen CH, Yang JY, Tsao CH, Shen CW, et al. Antibody-dependent SARS coronavirus infection is mediated by antibodies against spike proteins. Biochem Biophys Res Commun 2014; 451:208-14. [CrossRef]
13. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. Coronavirus infections and immune responses. J Med Virol 2020; 92:424- 32. [CrossRef]
14. Channappanavar R, Fehr AR, Zheng J, Wohlford-Lenane C, Abrahante JE, Mack M, et al. IFN-I response timing relative to virus replication determines MERS coronavirus infection out comes. J Clin Invest 2019; 130:3625-39. [CrossRef]
15. Snijder EJ, van der Meer Y, Zevenhoven-Dobbe J, Onderwater JJ, van der Meulen J, Koerten HK, et al. Ultrastructure and origin of membrane vesicles associated with the severe acute respiratory syndrome coronavirus replication complex. J Virol 2006; 80:5927-40. [CrossRef]
16. Cecere TE, Todd SM, Leroith T. Regulatory T cells in arterivirus and coronavirus infections: do they protect against disease or enhance it? Viruses 2012; 4:833-46. [CrossRef]
17. Zhao J, Li K, Wohlford-Lenane C, Agnihothram SS, Fett C, Zhao J, et al. Rapid generation of a mouse model for Middle East respiratory syndrome. Proc Natl Acad Sci USA 2014; 111:4970-5. [CrossRef]
18. Ganji A, Farahani I, Khansarinejad B, Ghazavi A, Mosayebi G. Increase dexpression of CD8 marker on T-cells in COVID-19 patients. Blood Cells Mol Dis 2020; 83:102437. [CrossRef]
19. Janice Oh HL, Ken-En Gan S, Bertoletti A, Tan YJ. Understanding the T cell immune response in SARS coronavirus infection. Emerg Microbes Infect 2012; 1:e23. [CrossRef]
20. Wang F, Nie J, Wang H, Zhao Q, Xiong Y, Deng L, et al. Characteristics of peripheral lymphocyte subset alteration in COVID-19 pneumonia. J Infect Dis 2020; 221:1762-9. [CrossRef]
21. Qin C, Zhou L, Hu Z, Zhang S, Yang S, Tao Y, et al. Dysregulation of immune response in patients with COVID-19 in Wuhan, China. Clin Infect Dis 2020; 71:762-8. [CrossRef]
22. Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C, et al. Pathological findings of COVID-19 associated with acute respiratory distress syndrome. Lancet Respir Med 2020; 8:420-2. [CrossRef]
23. Zhang W, Zhao Y, Zhang F, Wang Q, Li T, Liu Z, et al. The use of anti-inflammatory drugs in the treatment of people with severe coronavirus disease 2019 (COVID-19): The perspectives of clinical immunologists from China. Clin Immunol 2020; 214:108393. [CrossRef]
24. Grasselli G, Tonetti T, Filippini C, Slutsky AS, Pesenti A, Ranieri VM, et al. Pathophysiology of COVID-19-associated acute respiratory distress syndrome-author's reply. Lancet Respir Med 2021; 9:e5-6. [CrossRef]
25. Huang C, Wang Y, Li X, Ren L, Zhao J, Hu Y, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020; 395:497- 506. [CrossRef]
26. Lindsley AW, Schwartz JT, Rothenberg ME. Eosinophil responses during COVID-19 infections and coronavirus vaccination. J Allergy Clin Immunol 2020; 146:1-7. [CrossRef]
27. Yang Y, Shen C, Li J, Yuan J, Wei J, Huang F, et al. Plasma IP-10 and MCP-3 levels are highly associated with disease severity and predict the progression of COVID-19. J Allergy Clin Immunol 2020; 146(1):119-127.e4. [CrossRef]

28. Zhang Y, Yu L, Tang LL, Zhu M, Jin Y, Wang Z, et al. A Promising Anti-Cytokine-Storm Targeted Therapy for COVID19: The Artificial-Liver Blood-Purification System. Engineering (Beijing) 2021; 7:11-3. [CrossRef]

29. Odabasi Z, Cinel I. Consideration of Severe Coronavirus Disease 2019 As Viral Sepsis and Potential use of Immune Check point Inhibitors. Crit Care Explor 2020; 6:e0141. [CrossRef]

30. Kang S, Tanaka T, Narazaki M, Kishimoto T. Targeting interleukin-6 signaling in clinic. Immunity 2019; 50:1007-23. [CrossRef]

31. Choy E, Rose-John S. Interleukin-6 as a multifunctional regulator: inflammation, immune response, and fibrosis. J Scleroderma Relat Disord 2017; 2:S1-5. [CrossRef]

32. Spits H, Cupedo T. Innate lymphoid cells: emerging insights in development, lineage relationships, and function. Annu Rev immunol 2012; 30:647-75. [CrossRef]

33. Liu J, Li S, Liu J, Liang B, Wang X, Wang H, et al. Longitudinal characteristics of lymphocyte responses and cytokine profiles in the peripheral blood of SARS-CoV-2 infected patients. EBioMedicine. 2020; 55: 102763. [CrossRef]

34. Leng Z, Zhu R, Hou W, Feng Y, Yang Y, Han Q, et al. Transplantation of ACE2(-) Mesenchymal Stem Cells Improves the Outcome of Patients with COVID-19 Pneumonia. Aging Dis 2020; 11:216-28. [CrossRef]

35. Giamarellos-Bourboulis EJ, Netea MG, Rovina N, Akinosoglou K, Antoniadou A, Antonakos N, et al. Complex immune dysregulation in COVID-19 patients with severe respiratory failure. Cell Host Microbe 2020; 27:992-1000.e3. [CrossRef]

36. Zheng M, Gao Y, Wang G, Song G, Liu S, Sun D, et al. Functional exhaustion of antiviral lymphocytes in COVID-19 patients. Cell Mol Immunol 2020; 17:533-5. [CrossRef]

37. van Montfoort N, Borst L, Korrer MJ, Sluijter M, Marijt KA, Santegoets SJ, et al. NKG2A blockade potentiates CD8 T Cell immunity induced by cancer vaccines. Cell 2018; 175:1744-55.e15. [CrossRef]

38. Wang R, Xiao H, Guo R, Li Y, Shen B. The role of C5a in acute lung injury induced by highly pathogenic viral infections. Emerg Microbes Infect 2015: 2015; 4:e28. [CrossRef]

39. Maglakelidze N, Manto KM, Craig TJ. A review: Does complement or the contact system have a role in protection or pathogenesis of COVID-19? Pulm Ther 2020; 6:169-76. [CrossRef]

40. Vankadari N, Wilce JA. Emerging WuHan (COVID-19) coronavirus: glycan shield and structure prediction of spike glycoprotein and its interaction with human CD26. Emerg Microbes Infect 2020; 9:601-4. [CrossRef]

41. Huang IC, Bailey CC, Weyer JL, Radoshitzky SR, Becker MM, Chiang JJ, et al. Distinct patterns of IFITM-mediated restriction of filoviruses, SARS Coronavirus, and Influenza A Virus. PLoS Pathog 2011; 7: e1001258. [CrossRef]

42. Ulrich H, Pillat MM. CD147 as a target for COVID-19 treatment: suggested effects of azithromycin and stem cell engagement. Stem Cell Rev Reports 2020; 16:434-40. [CrossRef]

43. Retamal-Díaz A, Covián C, Pacheco GA, Castiglione-Matamala AT, Bueno SM, González PA, et al. Contribution of Resident Memory CD8+ T Cells to Protective Immunity Against Respiratory Syncytial Virus and Their Impact on Vaccine Design. Pathogens 2019; 8:147. [CrossRef]

44. Azkur AK, Akdis M, Azkur D, Sokolowska M, Veen W, Brüggen M, et al. Immune response to SARS - CoV - 2 and mechanisms of immunopathological changes in COVID-19. Allergy 2020; 75:1564-81. [CrossRef]

45. Palomares O, Akdis M, Martin-Fontecha M, Akdis CA. Mechanisms of immune regulation in allergic diseases:the role of regulatory T and B cells. Immunol Rev 2017; 278:219-36. [CrossRef]

46. Breedveld A, van Egmond M. IgA and FcαRI: Pathological Roles and Therapeutic Opportunities. Front Immunol 2019; 10:553. [CrossRef]

47. Temperton NJ, Chan PK, Simmons G, Zambon MC, Tedder RS, Takeuchi Y, et al. Longitudinally profiling neutralizing antibody response to SARS coronavirus with pseudotypes. Emerg Infect Dis 2005; 11:411-6. [CrossRef]

48. Iwasaki A, Yang Y. The potential danger of suboptimal antibody responses in COVID-19. Nat Rev Immunol 2020; 20:339-341. [CrossRef]

49. Tan W, Lu Y, Zhang J, Wang J, Dan Y, Tan Z, et al. Viral kinetics and antibody responses in patients with COVID-19. medRxiv 2020 [CrossRef]

50. Jin Y, Yang H, Ji W, Wu W, Chen S, Zhang W, et al. Virology, epidemiology, pathogenesis, and control of COVID-19. Viruses 2020; 12:372. [CrossRef]

51. Yin S, Huang M, Li D, Tang N. Difference of coagulation features between severe pneumonia induced by SARS-CoV-2 and non-SARS-CoV-2. J Thromb Thrombolysis 2020; 51:1107-10. [CrossRef]

52. Sun W, Wang BL, Liu BL, Zhao FC, Shi ZC, Guo WS, et al. Osteonecrosis in patients after severe acute respiratory syndrome (SARS): possible role of anticardiolipin antibodies. J Clin Rheumatol 2010; 16:61-3. [CrossRef]

53. Gupta N, Zhao YY, Evans CE. The stimulation of thrombosis by hypoxia. Thromb Res 2019; 181:77-83. [CrossRef]

54. Zhang Y, Xiao M, Zhang S, Xia P, Cao W, Jiang W, et al. Coagulopathy and antiphospholipid antibodies in patients with COVID-19. N Engl J Med 2020; 382:e38. [CrossRef]