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# COVID-19: Is it a SARS-CoV-2-Induced Dysregulated Inflammatory Response?

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## Abstract

COVID-19 can present with various clinical manifestations, in particular from mild to severe forms. Most patients have a good prognosis, while a small part develops severe disease. In patients with the most severe form of the disease, usually a week after the onset of symptoms, dyspnea and hypoxemia occur with the evidence of "ground glass" pneumonia at CT scan. COVID-19 patients show lymphopenia and peculiar anatomopathological changes: The spleen is reduced in size and above all, both the spleen and the lymphnodes show a reduction of both CD4+ T lymphocytes and CD8+ lymphocytes on immunohistochemical tests. Moreover, COVID-19 would appear to be characterized by a dysregulated inflammatory response and this condition would be confirmed by the efficacy of some immunomodulatory treatments, such as Tocilizumab and Hydroxychloroquine. But which causes this dysregulated inflammatory response? In light of the alterations found in the SARS-CoV-2 infection and of the same mechanism of action of the virus, it could be hypothesized that the virus interferes directly with the acquired immune response.

**Keywords: SARS-CoV-2; COVID-19; Inflammatory response, Innate immune response, Acquired immune response**

## Introduction

In recent months, the encounter with a new enemy has been surprising and is upsetting our daily lives; this enemy has the name of SARS-CoV-2 (Severe Acute Respiratory Syndrome - Coronavirus-2). SARS-CoV-2 is the causative agent of COVID-19 (Coronavirus Disease-2019). The main manifestations of COVID-19 are fever, dry cough and asthenia. In a minority of patients, there is a feeling of nasal obstruction, rhinorrhea, pharyngodynia, myalgia and diarrhea [1]. In patients with severe form of the disease, usually a week after the onset of symptoms, dyspnea and hypoxemia occur with the evidence of "ground glass" pneumonia at CT scan [2,3]. Rapid progression to ARDS (Acute Respiratory Distress Syndrome), septic shock, metabolic acidosis, coagulation deficiency and lastly MOF (Multiple Organ Failure) is possible in critically ill patients [4,5]. According to the cases treated so far, most patients have a good prognosis, while a small part develops severe disease. The oldest patients and the ones with concomitant comorbidities have a worse prognosis [6]. Laboratory tests show, in the initial phase of the disease a normal or slightly reduced White Blood Cell (WBC) count. However, regardless of whether or not leukopenia is found, what characterizes these patients is the appearance of lymphopenia. Some patients may present elevated transaminases, Lactate Dehydrogenase (LDH), Creatine Kinase (CPK) and myoglobin. Severe patients may have Troponin T Elevation (TnT). In most cases, an increase in C Reactive Protein (CRP) and Erythro-Sedimentation Rate (ESR) is observed, in the absence of an increase in Procalcitonin (PCT) [7,8]. Patients with severe course of the disease often have an increase in inflammatory cytokines. Radiologically, in the initial phase of the disease, a nodular and/or interstitial pattern occurs, especially in the periphery of the parenchyma. Subsequently, ground glass patterns and infiltrative patterns develop bilaterally while pleural effusion is infrequent [9]. The described anatomopathological changes are surprising, despite they resulted from the limited autopsy studies and from the observation of biopsy specimens. The lungs can have different degrees of consolidation. In the alveoli serum and fibrin can be found, the inflammatory cells mainly found are monocytes and macrophages and often also polymorphonucleated neutrophils. There is hyperplasia of type II pneumocytes with associated de-epithelialization. Inclusion bodies may be present inside type II pneumocytes and macrophages. The pulmonary parenchyma has focal hemorrhages and necrosis, up to a hemorrhagic infarction in some cases. The exudate present in a part of the alveoli can consolidate and the pulmonary fibrosis can occur [8]. Viral particles can be observed under the

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electron microscope inside the cytoplasm of the epithelial cells of the bronchial mucosa and type II pneumocytes. Immunohistochemical examination can highlight viral antigens in a part of epithelial cells and macrophages, while RT-PCR (Real-Time Polymerase Chain Reaction) can detect the presence of the virus' nucleic acids. Cardiomyocytes can present cell degenerations and necrosis, and some monocytes, lymphocytes and/or polymorphonuclear neutrophils can be observed in the interstitium [8]. In kidney biopsies, fibrinous exudate is formed in the Bowman's capsule, the renal tubules present epithelial degeneration and de-epithelialization. In the interstitium the capillaries are hyperemic, with possible micro-thrombi, and interstitial fibrosis can occur. The cerebral parenchyma presents hyperemia and edema with degeneration of a part of the neurons. The adrenals present focal necrosis. The esophageal, gastric and intestinal mucous membranes present, with varying degrees, degenerations, necrosis and de-epithelialization. In liver biopsies it has been demonstrated that hepatocytes degenerate, present cell necrosis in the presence of neutrophilic infiltrate. The liver sinusoids are hyperemic with possible micro-thrombi and lymphocyte and neutrophil infiltrate in the portal spaces. The spleen is reduced in size, may present with bleeding and focal necrosis. Lymphocytes decrease considerably in number and go into necrosis and macrophages proliferate with phagocytic phenomena. On immunohistochemical tests, the spleen and lymphnodes show a reduction in CD4+ and CD8+ T lymphocytes. In the bone marrow, the cells of all three lines (erythroid, myeloid and megakaryocyte) are reduced in number [8]. Based on the foregoing, what is surprising is the fact that the spleen is reduced in size and above all, both the spleen and the lymphnodes show a reduction of both CD4+ T lymphocytes and CD8+ lymphocytes on immunohistochemical tests as if the acquired immune response is damaged. At the same time what is observed is a significant increase in monocytes, macrophages and often polymorphonucleated, as observed by autopsy studies and the observation of biopsy samples on lung tissue. This is consistent with the finding of a significant increase in pro-inflammatory cytokines in blood [7,8].

## Discussion

From these preliminary clinical-laboratory data, it could be assumed that SARS-CoV-2 could interfere with the acquired immune response, preventing the latter from carrying out its task. At the same time, it could be hypothesized that the lack of specific acquired immune response could lead to an increase of the innate immune response, which would lead, in turn, to an excessive and dysregulated inflammatory response [10]. Given this, our immune system, to effectively protect the individual against infection, should perform four main steps. The first is immunological recognition: The presence of an infection should be identified. This step is performed by the white blood cells of the innate immune system, which provide an immediate response. The second moment is to contain the infection and if it is possible to eliminate it completely. This action involves immune effector functions, such as the complement system of blood proteins, antibodies and the destructive capacities of lymphocytes and other white blood cells. At the same time, the immune response should be kept under control, so that it does not harm the body by itself (friendly fire). Immune regulation, or the ability of the immune system to regulate itself, is thus an important feature of immune responses, and the defective functioning of this regulation favors the onset of a dysregulated immune response. The last step is the protection of the individual from the recurrence of the disease caused by the pathogen itself. A characteristic of the acquired immune system is the ability to generate immunological memory, so that after being exposed to an infectious agent an individual develops an immediate and stronger response against any subsequent exposure to the same agent [11,12]. Let's start from the beginning. When an individual first encounters an infectious agent, the first cells involved in the immunological response are leukocytes - phagocytes, like macrophages, which are part of the innate immune system. These cells are capable of ingesting and killing microbes producing various toxic chemicals and powerful degrading enzymes [13]. The innate immune response occurs immediately after exposure to the infectious organism, while the acquired immune system, which overlaps the innate immune response, but which needs to develop for days rather than hours, is capable of eliminating infections with greater effectiveness than the innate immune system. The response acquired depends on the extremely specific recognition functions of lymphocytes, which have the ability to recognize the particular pathogen and focus the immune response on it more effectively. The acquired-specific immune response would thus allow to concentrate the resources of the immune system in fighting this pathogen [14]. Now most of the infected agents activate the innate immune system and induce an inflammatory response, in particular the macrophages found in the tissues are the first line of defense, they recognize by means of receptors the constituents of many surfaces of the microorganisms. Like macrophages, neutrophils have receptors for recognition on the surface and play an important role in engulfing and destroying pathogenic microorganisms [15]. The influx of neutrophils followed shortly after that of monocytes that quickly differentiate into macrophages, strengthening and supporting the innate immune response [16]. The binding to these receptors stimulates the macrophage to engulf the microorganism and to degrade it internally, and to secrete proteins called cytokines and chemokines. These cytokines and chemokines released by activated macrophages begin the process known as inflammation [17]. Inflammation of an infected tissue has several beneficial effects for fighting infection. It recruits the cells and molecules of innate immunity outside the circulation and inside the tissue, where they are needed to immediately destroy the pathogen. It also increases the flow of lymph that carries the microorganisms and cells that present the antigen to nearby lymphoid tissues, where they will activate the lymphocytes and start the acquired immune response [18]. On the other hand, induction of the acquired immune response begins when a pathogen is ingested by an immature dendritic cell present in the infected tissue [19]. These specialized phagocytic cells are present in most tissues and like macrophages and neutrophils, immature dendritic cells have specific receptors on their surface that recognize pathogens. The binding of microbial components to these receptors stimulates dendritic cells to engulf the pathogen and degrade it inside the cell. Immature dendritic cells also continue to capture extracellular material, including bacterial and viral particles, through a receptor-independent mechanism called macropinocytosis, and are thus able to internalize and degrade pathogens that their cellular surface receptors cannot detect. However, the main function of dendritic cells is not to destroy pathogens, but to bring pathogen antigens to peripheral lymphoid organs to present them to T lymphocytes [20]. Activation of naive T lymphocytes is an essential first stage for triggering acquired immune responses [21]. Now, we hypothesize that at this level there is interference from SARS-CoV-2, which could induce an alteration by the immune system; in particular the virus would interfere with the normal development and evolution of the acquired immune response. This hypothesis could be supported by

the fact that in order to infect human cells, SARS-CoV-2 uses the viral protein 'spike' (or "S") that binds to the human ACE-2 receptor (Angiotensin Converting Enzyme-2) [22]. ACE-2 therefore becomes the entry point into human cells for the SARS-CoV-2 virus. This receptor is expressed by different types of cells; in particular it is expressed by vascular endothelial cells, renal tubular epithelium, Leydig cells in the testes. ACE-2 is also expressed in smooth muscle cells and macrophages [23]. PCR analysis revealed that ACE-2 is also expressed in the lung, kidney, and gastrointestinal tract, tissues shown to harbor SARS-CoV [24-26]. ACE-2 is a type I transmembrane metallocarboxypeptidase with homology to ACE, an enzyme long-known to be a key player in the Renin-Angiotensin System (RAS) and a target for the treatment of hypertension [27,28]. Zhou et al. [29] showed that SARS-CoV-2 could use ACE-2 to gain entry into ACE-2-expressing HeLa cells. Hoffmann et al. [30] reported similar findings for human and bat ACE-2. Additionally, Hoffmann et al. [30] showed that treating Vero-E6 cells, a monkey kidney cell line known to permit SARS-CoV replication, with an Anti-ACE-2 Antibody (R&D Systems, Catalog # AF933), entry of pseudotypes expressing the SARS-CoV-2 S protein was blocked. Considering the foregoing and considering that the ACE-2 receptor is expressed on macrophages and especially on dendritic cells, this could explain the potential mechanism underlying the interference with the acquired immune response. In other words, the virus could directly affect the dendritic cells and induce a lack of signal for the activation of T lymphocytes. This lack of activation could explain lymphopenia and, above all, the lack of development and activation of peripheral lymphoid organs, such as spleen and lymph nodes, found by autopsy surveys. Failure to respond to an acquired immune response could result in a persistence of the innate immune response and consequently the persistence of an inflammatory response that in an unspecific way, in an attempt to deal with the virus, would amplificate damage [31,32]. It could be hypothesized that a dysregulated inflammatory response could be the basis of the severe evolution of some clinical condition. Actually, this hypothesis could be supported and could be confirmed by the fact that more or less during the ninth day of the course of the disease, a deterioration of clinical condition may occur with the finding of pneumonia characterized by interstitial commitment and consolidations [33,34]. The clinical worsening in this moment of the course of the disease could be justified by the expected timing of the intervention of the acquired immune response which could be damaged, with the occurrence of a dysregulated inflammatory response [35]. The persistence of innate immunity and the consequent dysregulated inflammatory response could be confirmed by the fact that high levels of pro-inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1α, and TNFα have been found in these categories of patients that are reasoned to promote disease severity. And probably, this very dysregulated inflammatory response could explain the severe evolution of the disease. At the same time, this hypothesis could explain the efficacy of recently available drugs, such as Tocilizumab [36]. Tocilizumab is a monoclonal antibody that blocks the IL-6 receptor and given the clinical and cytokine status in patients with severe COVID-19 pneumonia, tocilizumab could have a rational for blocking the SIRS (Systemic Inflammatory Response Syndrome) caused by the virus in patients with high IL-6 levels. In China, in the Anhui Province Hospital, a trial is underway for the use of Tocilizumab in the PCN (ChiCTR 2000029765); the expected dosage is 8 mg/kg to be repeated after 12 h. Conversely, the dosage used by Xiaoling Xu in a Chinese pilot study (Effective Treatment of Severe COVID-19 Patients with Tocilizumab, in press) was 400 mg iv in single dose with a possible second dose if no clinical response was received; this study shows promising results in 21 patients treated with significant reduction of IL-6 and fever with improvement in lung function [37,38]. Moreover, together with IL-6 also chloroquine and hydroxychloroquine have been prescribed in patients affected by COVID-19. Actually, chloroquine can exert direct antiviral effect by increasing the endosomal pH necessary for the fusion virus/host cell. Furthermore, chloroquine appears to interfere with the glycosylation of SARS-COV-2 cell receptors. Chloroquine also has immunomodulatory activity, which could amplify antiviral activity *in vivo* [39-41].

## Conclusion

It can be hypothesized that at the basis of COVID19 pathogenesis, there is a dysregulated inflammatory response induced by SARS-CoV-2 itself. SARS-CoV-2 could precisely interfere directly with the immune response, in particular with the acquired immune response, inducing an alteration of this type of immunity. This action could in turn induce a dysregulated inflammatory response, which in turn is responsible for the parenchymal damage induced and the severe evolution of the clinical condition. However, what has been said and hypothesized needs to be experimentally demonstrated.

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