International Archives of Medical Research 14:1 (2022) 30-38

REVIEW

COVID-19 Associated Autoimmunity: "Are Autoantibodies Neglected?"

Received Date: 31.10.2022, Accepted Date: 23.12.2022 **DOI: 10.56484/iamr.1197191**

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Özet:

Koronavirüsler soğuk algınlığı gibi hafif enfeksiyon tablolarından, daha ağır klinik tablolara neden olabilen büyük bir virüs ailesidir. 31 Aralık 2019'da Çin'in Wuhan şehrinde etiyolojisi bilinmeyen pnömoni vakaları bildirilmiştir. 7 Ocak 2020'de hastalığın adı Coronavirus Disease-2019 (COVID-19) , etkenin adı da SARS-CoV-2 olarak adlandırılmıştır. Araştırmalar, hastalığın kötüleşmesinin immünopatolojik olduğunu göstermiştir. Virüse karşı şiddetli bir immünolojik yanıtın başlaması ve sitokin seviyelerinin yükselmesi sonucu klinik progresyon hızlıca kötüleşmektedir. Şiddetlenen immünolojik yanıtın yanı sıra, bazı çalışmalarda otoantikorların hastalığa etkisi üzerinde durulmuştur. Bazı hastalarda kendi hücre ve dokularını hedef alan otoantikorlar rapor edilmiştir. Bu otoantikorların nasıl oluştuğu tam olarak bilinmese de, immün sistemin kişinin kendi hücrelerine karşı duyarlılaşması ve virüse ait epitoplardan bazılarının kendi antijenlerimizle benzerlik gösterebileceği teorileri üzerinde durulmaktadır. Otoantikorların hastalığın şiddetini arttırarak iyileşme sürecini uzattığı gösterilmiştir. COVID-19 vakalarında en sık (Anti-nükleer antikor) ANA, anti-fosfolipid antikorları ve anti-tip 1 interferon antikorları saptanmıştır. Nadiren diğer otoantikortürlerine de (Anti-nötrofil sitoplazmik antikor (ANCA), Anti-siklik sitrullin peptid antikor (Anti-CCP) vb.) rastlanmıştır. COVID-19 hastalığında otoantikorların oluşumu ile ilgili ileriye yönelik daha çok sayıda bilimsel araştırma yapılması gerekmektedir.

Anahtar kelimeler : *COVID-19, SARS-CoV-2, Otoantikorlar, Anti-Nükleer Antikorlar, Anti-Nötrofil Sitoplzmik Antikorlar*

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Abstract:

Coronaviruses are a large family of viruses that can cause mild infections, such as the common cold, to more severe clinical manifestations. On 31 December 2019, cases of pneumonia of unknown etiology were reported in Wuhan, China. On 7 January 2020, the name of the disease was named Coronavirus Disease-2019 (COVID-19), and the agent was named SARS-CoV-2. Studies have shown that the worsening of the disease was immunopathological. Clinical progression rapidly worsens as a result of the onset of a severe immunological response to the virus and the elevation of cytokine levels. In addition to the intensified immunological response, some studies have focused on the effect of autoantibodies on the disease. Autoantibodies targeting their own cells and tissues have been reported in some patients. Although it is not known exactly how these autoantibodies are formed, theories are focused on the sensitization of the immune system to one's own cells and that some of the epitopes of the virus may resemble our antigens. Autoantibodies have been shown to increase the severity of the disease and prolong the healing process. (Anti-nücleer antibody) ANA, anti-phospholipid antibodies and anti-type 1 interferon antibodies were detected most frequently in COVID-19 cases. Rarely, other types of autoantibodies -Anti-neutrophil cytoplasmic antibody (ANCA), Anti-cyclic citrulline peptide antibody (Anti-CCP) etc.- have been encountered. More comprehensive prospective scientific studies should be conducted on the formation of autoantibodies in COVID-19 disease.

Keywords : COVID-19, SARS-CoV-2, Autoantibodies, Anti-Nuclear antibodies, Anti-Neutrophil Cytoplasmic Antibodies

Introduction

Coronaviruses (CoV) are a collection of viruses that can cause mild infections, usually in the form of the common cold. SARS-CoV (Severe Acute Respiratory Syndrome Coronavirus) first detected in humans in 2002 and MERS-CoV (Middle East Respiratory Syndrome Coronavirus) in 2012 caused fatal epidemics [1,3,6]. The third coronavirus epidemic in the world started with the notification of pneumonia cases of unknown cause in Wuhan, China by the World Health Organization (WHO) in December 2019. Later, the name of the disease was accepted as Coronavirus Disease-2019 (COVID-19) and the agent was named SARS-CoV-2. The first COVID-19 case in our country was seen on March 11, 2020 [1]. The World Health Organization declared the epidemic as a pandemic on March 11, 2020 [2].

Virological Characteristics of SARS-CoV-2

Coronaviruses are enveloped single-stranded RNA viruses in the Coronaviridae family. These viruses are named Coronavirus due to the presence of protrusions on their surfaces called “corona”, meaning “crown” in Latin [3,4]. SARS-CoV-2 is in the Betacoronavirus genus. The genetic structure of this genus was shown to be similar to the genome of the bat-derived coronavirus [5].

Pathogenesis of COVID-19: "What's going on in the immune system?"

The pathogenesis of COVID-19 can be examined under three headings: virus proliferation, overstimulation of the immune system and multi-organ failure [7]. First, the virus replicates in host cells and infects new cells, causing damage to the lung parenchyma. In addition, acute respiratory distress syndrome (ARDS), sepsis, and multi-organ failure develop as a result of excessive cytokine production by over-stimulating the immune system [8,9]. Some studies show that a severe immune response is more important than a direct virus-specific lethal effect in COVID-19 [10]. Thus, with the progression of the disease, the overstimulation of the immune system and the serious increase in cytokine levels indicate that serious organ damage may be of immunopathological origin [11,12].

COVID-19 Immunopathogenesis

Studies have shown that the Coronavirus Spike protein is an important structural fragment for the virus to enter target cells [13]. This molecule enters the cell by binding to the Angiotensin converting enzyme-2 (ACE-2) receptor on the target cell surface [14,15]. Then, the virus RNA is released into the cytoplasm and all the structures belonging to the virus are synthesized. The resulting viruses are released out of the cell by budding [14,16-18]. Lung epithelial cells begin to secrete interleukin-8 (IL-8), which has a stimulating effect on neutrophils and T lymphocytes [19]. The innate immune response is initially induced by lung epithelial cells, alveolar macrophages, and neutrophils. Afterwards, T and B lymphocytes take part[20].

RNA-containing viruses are recognized by macrophages and initiate the innate immune response. This causes the synthesis of IL-1, IL-6 and Type 1 interferon (IFN1) [21]. In addition, neutrophils work towards the infection site to destroy the virus [22]. As a result of antigen presentation, abundant cytokines begin to be synthesized. Antigen-specific cytotoxic T lymphocytes destroy infected cells, while B cells produce virus-specific antibodies [23,24]. As in other viral infections, virus-specific IgM and IgG-type antibodies are formed. IgG antibodies that are specific to the virus are of the protective type [25]. It has been shown that IgG and IgM levels are higher in severe cases than in mild cases [26]. In addition to these specific antibodies in COVID-19 patients, the formation of autoantibodies, which can increase the severity of the disease by attacking some cells and tissues, has also been a matter of curiosity.

What is Autoantibody? Why does it occur?

The most important feature of a normal immune system is that while immune system cells respond to many foreign antigens, they do not respond to their own antigens. Thanks to this discrimination ability, while immune system cells attack microorganisms, no defense response occurs against the body structures. Our immune system acquires this feature, called immune tolerance, in the bone marrow and thymus while still in the mother's womb. Meanwhile, T and B lymphocytes that respond to the body's self-antigen are eliminated by various mechanisms [27]. This tolerance mechanism is called central tolerance. Another mechanism is the peripheral tolerance mechanism [28]. Central tolerance is achieved in two ways. First, immune-reacting cells are destroyed by apoptosis when self-antigen is presented to them. The second is the expression or anergy (reducing receptor expression) of a new Fab receptor that does not respond when bound to self-antigen. Thus, autoreactive cells are destroyed during the construction phase. However, if the central tolerance mechanism cannot function completely, some T and B lymphocytes may manage to escape this mechanism [29]. In this case, escaping autoreactive lymphocytes are destroyed by the other mechanism, peripheral tolerance. Peripheral tolerance occurs in lymph nodes and tissues. Here, autoreactive lymphocytes are inactivated by mechanisms such as apoptosis and anergy. Peripheral tolerance functions in this way and acts as a second defense mechanism [30].

Thanks to tolerance mechanisms, although a healthy individual tries to protect own antigens from own immune system, unresponsiveness to own antigens may disappear in some cases. Some of the immune system cells do not recognize their own tissue antigens and begin to perceive them as a foreign antigen, and these cells attack the individual's own cells and tissues [31]. This condition is called **autoimmunity**, and antibodies against self antigen are called **autoantibodies**. Autoantibodies can damage various structures in the body, either intracellular or extracellular. For example, antinuclear antibodies (ANA) to structures such as DNA, RNA, nucleolus in the cell nuclei of all systems in the body, anti-phospholipid antibodies to the circulatory system by affecting the phospholipids in the cell membrane, Anti-neutrophil cytoplasmic antibodies (ANCA) to neutrophils and therefore to the vessels, parietal cell antibodies to the stomach, thyroglobulin antibody to the thyroid gland, acetylcholine receptor antibody damages the muscles [32,33]. It has also been reported that autoantibodies can be formed against cytokines [34].

Although it is not known exactly why autoimmunity is triggered, some possibilities are being considered. One of these is the introduction of an antigen that cross-reacts into the organism. Antibodies produced against these antigens are thought to respond to self-antigens after a while

[35,36]. The second possibility is that some drugs and chemicals affect immune system cells and some chronic infections cause changes in the body's own antigens. These structural changes in self-antigens cause the immune system cells to give autoreactive responses [37]. A third possibility is failure of immune tolerance due to genetic causes (especially Major Histocompatibility Complex (MHC) genes). When this process is insufficient, autoantibody formation is triggered [38]. In addition, T lymphocyte dysfunction may also cause autoantibody formation. In this case, T lymphocytes cause B lymphocytes to produce antibodies against self-antigens that they see as foreign [39].

COVID-19 Associated Autoantibodies

In the COVID-19 disease caused by the SARS-CoV-2 virus, which was identified at the end of 2019, the immune system interferes with this situation when the virus enters the body. Virus-specific antibodies are rapidly produced. It is known that first IgM levels increase and then IgG antibodies increase. These antibodies help to heal by playing an important role in the fight against the virus [40]. However, in some patients, apart from the antibodies produced specifically for the virus, autoantibodies targeting their own cells and tissues were also found [41]. Although it is not known exactly how these autoantibodies are formed, two possibilities are considered. The first is that in repeated coronavirus infections, the immune system becomes so sensitized that it damages one's own cells. Second, some of the epitopes of the virus are similar to our own antigens. It is thought that some of the antibodies formed against the virus in this way also damage our cells [35]. It has been observed that the autoantibodies formed are one of the important factors affecting the severity of the disease. Autoantibodies have been held responsible for severe symptoms that may even lead to death in some patients [42]. It has been reported that ANA, antiphospholipid antibodies and anti-type 1 interferon antibodies are most frequently encountered in COVID-19 cases, as well as other types of autoantibodies rarely [35].

Anti-Nuclear Antibody (ANA)

ANA is a common autoantibody in autoimmune diseases such as Systemic Lupus, Sjögren's and Systemic Sclerosis. These autoantibodies attack structures such as DNA, histones, and centromeres in the cell nucleus, causing widespread tissue damage and inflammation. It is the most common type of autoantibodies in COVID-19 patients. ANA was reported positive in approximately **40-50%** of the patients [43,44]. In addition, a relationship was stated between disease severity and ANA level [45]. While the ANA level was found to be high in those with severe disease, lower levels of ANA were detected in those with mild disease. Although approximately 10% of healthy people may also have ANA, this high rate indicates that COVID-19 triggers autoimmunity.

Antiphospholipid Antibodies

Phospholipids are compounds found in the membranes of all cells, including blood cells and endothelial cells that line the vessel wall. Antiphospholipid antibodies target these compounds. It is thought that these antibodies, which attach to the phospholipids in the cell membrane, initiate coagulation [46]. These autoantibodies have been blamed for disseminated intravascular coagulation in critically ill COVID-19 patients, and thrombosis has had serious consequences that can lead to death [47].

Anti Type 1 Interferon Antibodies

Type 1 interferons are antiviral cytokines that function in the immune system. They are synthesized by fibroblasts and monocytes to prevent virus attack. Type 1 interferons bind to specific receptors on target cells, resulting in the formation of proteins that prevent the replication of viruses within the cell. Thus, the proliferation of the virus in the cell is prevented and the spread of the virus to other tissues is prevented [48]. In particular, autoantibodies against type 1 interferons were found in approximately 10% of patients with severe COVID-19 [42]. It is thought that these autoantibodies bind to type 1 interferons, preventing their function and accelerating the spread of the virus. Therefore, it was concluded that one of the reasons for having a severe disease may be due to the presence of anti-type 1 interferon antibodies. It has also been observed that these autoantibodies affect on the disease in healthy young people [49].

Conclusıon

Autoantibodies have been found at a lower rate in COVID-19 patients than in other diseases. These autoantibodies have been shown to increase the severity of the disease and prolong the healing process. On the other hand, it has been found that a large amount of autoantibodies formed during the disease period can remain in the body for a long time after the disease [41]. This shows us that the effects of autoantibodies can continue even after the disease has healed. In rare cases, it has been found that autoantibodies may form after a certain period of time after the disease has healed [50]. For this reason, even if the pandemic ends, it would not be correct to say that the effects of the disease will disappear completely.

In recent years, case reports have been reported that SARS-CoV-2 vaccines also cause autoantibody formation [51]. The fact that approximately 85% of the population in our country is vaccinated makes the data of these studies valuable. Although vaccination has the risk of developing autoantibodies, a large community immunity has been created in the world with this practice, the number of intensive care patients and the stress caused by the pandemic on nations have decreased. For this reason, we think that the necessity of vaccinations is not open to

discussion. However, we believe that further scientific research is needed to determine whether SARS-CoV-2 and vaccinations cause autoantibody formation.

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