SARS-COV-2 AND AUTOIMMUNE RHEUMATIC DISEASES

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Abstract. Coronaviruses have been known to mankind for decades, accounting for about a third of flu-like illnesses each year in the early fall-winter period. At the end of 2019, a new coronavirus (SARS – CoV-2) was found, which in March 2020 was declared pandemic by the World Health Organization (WHO). The structure of the new virus continues to be studied, but the S-protein has been shown to play a major role in the pathogenesis of the disease it causes. Using the S-protein a host is attached to the cell. The severity of COVID-19 varies from individual to individual, but the main risk factors are age, sex, comorbidities and etc. At present, the question of whether the patients with autoimmune disease are at greater risk of severe COVID-19, remains unclear. The development of an effective vaccine give hope to society, but also raises a number of questions about long-term safety.

Key words: SARS-CoV-2, autoimmune rheumatic diseases

In late 2002, a case of severe fatal respiratory infection of unclear etiology was reported in Guang Zhou Province, China. The causative agent was subsequently identified, a hitherto unknown coronavirus called 'severe acute respiratory syndrome' or SARS. Coronaviruses are known as zoonoses (infect animals), but a possible mutation leads to their ability to infect humans as well. The analysis of SARS-Cov-2 found many similar epitopes to bats' coronaviruses, so they are the presumed primary source of infection in humans, due to the proximity of humans to wild-life in China. Infection with SARS-CoV in 2002-2003 was quickly controlled, with 8096 people infected and 774 deaths, according to the WHO, with a mortality rate of 9.6%.

In 2012, a case of severe respiratory distress syndrome was first described in humans in Saudi Arabia, with a new cause identified, a coronavirus called "Middle East respiratory syndrome" (MERS-CoV). It is believed that the primary source of infection was a bat, which transmitted the virus to camels, and through the proximity of the Arabs to camels, it was transmitted to humans. The epidemic in 2015 infected 186 people, of whom 36 died, it is estimated that the mortality rate from MERS-CoV is about 34%.

In late 2019, numerous cases of severe, rapidly developing respiratory infection with a potentially fatal outcome of unknown cause were reported in Wuhan, Hubei Province, eastern China. The epidemiological history of the patients connects them with the „wet market“ in the city. In December 2019, the causative agent was identified, a new, unknown

coronavirus named SARS-CoV-2 causing a new disease with acute respiratory distress syndrome called COVID-19. The primary source of infection is thought to be a bat that transmits the virus to another wild animal that is in close contact with humans.

In January 2020, soon after the isolation of the causative agent of severe respiratory syndrome in Wuhan, the genetic information of the pathogen was decoded, and scientists found that in about 90% it coincides with the known SARS, but is a new, hitherto unknown coronavirus called SARS-CoV-2 or WH-Human 1 coronavirus. [1] It is a particle with a diameter of 65-125 nm [2] containing one RNA molecule with 29.9 kb.

Fig. 1. SARS-CoV-2

At present, the transmission chain is not well studied, but it has been proven to be transmitted from person to person by airborne and contact route (sneezing and coughing) at a distance of about 2 m [3, 4]. Also, contact with contaminated surfac-

es could lead to contamination. The most likely front door for COVID-19 is the mouth and nose. It has been suggested that infection may also occur by eye contact. According to national and international guidelines for protection against coronavirus infection, it is recommended to wear personal protective equipment, such as masks, gloves, goggles and more. According to the US FDA (Food and Drug Administration), N95-certified respiratory protective masks filter airborne particles to 0.3 microns or 300 nm. The dimensions of COVID-19 are significantly smaller, which means that the highest class protective masks are not effective in this case. Standard surgical masks do not provide any protection against coronavirus infection.

At present, the mechanisms of transmission through the skin, blood and sex are not well studied. The virus has been shown to be present in semen and cervical fluid, as well as in faeces, but its concentration and contagiousness are unknown.

The data in the scientific literature for the incubation period of COVID-19 are diverse. Cases ranging from a few hours to 54 days have been described. Several of the leading health organizations issue their own opinion on the incubation period of COVID-19 – WHO (World Health Organization) 2-14 days, for the Chinese NHC (National Health Commission) it is 10-14 days, the American CDC (Centers for Disease Control and Prevention) 2-14 days. When analyzing the data of 10,000 infected people in China, in 95% of cases the first symptoms develop in 5.1 days, and in a period of 11.5 days, 97.5% of patients already have the disease [5].

The viral particle is made up of several proteins – S (spike), M (membrane), E (envelope) and one nucleocapsid N, which envelops the RNA molecule. The best studied is the S-protein, which builds the spikes of the virus and plays a key role in its pathogenicity. It contains a specific epitope called RBD (Receptor-Binding-Protein), which is recognized by the ligand of the host cell, as well as by T- and B-cells, which in turn produce neutralizing antibodies [4]. The S-protein is a trimeric glycoprotein that protrudes from the viral membrane and forms the specific crown, hence the name of the viral group. The S-protein is composed of two subunits, S1 and S2, which are responsible for the penetration of the virus into the host cell [3, 4, 5, 6, 7, 8, 9, 10]. The major receptor for virus entry into the host cell is ACE2 (Angiotensin 2 Converting Enzyme), a metalloprotease present on the membrane of a number of cells, such as pneumocytes. type I and II, enterocytes in the small intestine, cells in the proximal tubules of

the kidneys, smooth muscle cells in the arterial wall, etc [11, 12]. The interaction of RBD with ACE2 leads to structural changes in the S-protein and carries out the penetration of viral RNA into the target cell [3, 5, 13, 14, 15].

The clinical picture of COVID-19 varies widely, with about 80% of infections asymptomatic and undocumented. Nearly 15% of the disease is severe, often requiring hospitalization and intensive care. The severity of the clinical picture of COVID-19 is determined by a number of factors, such as age, sex, concomitant diseases and others. The reasons for the pronounced differences in the clinical picture in patients are still not well studied, but diseases such as diabetes, cardiovascular, oncological, autoimmune and others, are associated with a more severe course and significantly higher mortality. The viral load is also associated with the severity of the clinical picture in patients with COVID-19 [16, 17, 18, 19, 20].

Most commonly, SARS-CoV-2 penetrates the respiratory system through microscopic aerosols or contaminated surfaces containing viral particles. Reaching the bronchioles and alveoli, the main target of the virus are type-II ACE2+ pneumocytes, inducing their autophagy and secretion from the basement membrane, and inhibition of ACE2 expression. One of the main antiviral mechanisms in the early stages of infection is the synthesis of type I and III IFN, as SARS-CoV-2 has the ability to block. After the release of a large number of viral particles in the apoptosis of the infected cell, it leads to the invasion of the neighborhood, as well as viremia, which is the cause of the involvement of large ACE2+ cells in various organs [21, 22, 23, 24].

Congenital immunity plays a major role in the development of COVID-19. After the virus enters the host cell, it is recognized by specific receptors PRR (pattern recognition receptor), TLR7, TLR8, from some innate immune cells, such as alveolar macrophages [25]. PRR receptors play a key role in SARS-CoV-2, they affect some transcriptional factors such as IRF (interferon regulatory factor), NF- κ B and AP1 as a result of which the synthesis of interferon I and III, and some chemokines with powerful antiviral action is reduced [26]. Thus, the coronavirus influences the immune response, as chemokines are a potent attractant for various immunocompetent cells, such as polymononuclear cells, NK, dendritic, monocytes, and others. cells [27, 28]. At the same time, SARS-CoV-2 increases the synthesis of a large number of pro-inflammatory cytokines, such as IL-6, MCP1, CXCL1, CXCL5, CXCL10/IP10, and others.

In the pathogenesis of COVID-19, in addition to innate immunity, a major role is played by the acquired one, which is the basis of the hyper-inflammatory immune system [29, 30, 31, 32]. Protective immunity is exercised by T cells, with CD4+ providing information to B-cells that produce neutralizing antibodies, and CD8 cells phage the infected cells. The pathogenicity of SARS-CoV-2 is due to the fact that nearly 80% of infiltrated cells are CD-8 [33].

The combination of immune disorders that lead to the inability of the macroorganism to inhibit virus replication, block the phaging of infected cells, and overexpression of proinflammatory cytokines causes the acute inflammatory response and cytokine storm that underlie severe clinical CID.

The antibody immune response is primarily directed to the S-protein, thus blocking the binding of the virus to ACE2+ cells [34]. Much is still unknown regarding the antibody response to SARS-CoV-2, as well as cross-reactivity with other coronaviruses.

Teng and colleagues studied 2,000 people with COVID-19 and autoimmune diseases, finding little immunological overlap with antibodies to SARS-CoV-2 [35]. They found that some antibodies associated with autoimmune rheumatic diseases, such as rheumatoid factors (RF), lupus-specific, and antibodies to Sjögren's syndrome, could give a false-positive result for SARS-CoV-2 [35]. Some conditions, such as congenital hypogammaglobulinemia, may give a false-negative result [36].

Currently, there are about 100 million infected with the new coronavirus worldwide, more than 2 million are dead, and the mortality rate is about 3%. Given the pandemic nature of the spread of COVID-19, it

is inevitable that people with rheumatic autoimmune diseases will be affected. There are always a number of issues with morbidity and mortality among these patients. According to COVID-19 Global Rheumatology Alliance, there are nearly 14,000 rheumatic patients with proven COVID-19 worldwide.

According to EULAR data, as of January 5, 2021, there were 4,373 patients among the rheumatic patients in the COVID-19 registry, and 1,801 people were hospitalized or 41%. This is a significantly higher percentage compared to the general population, where the share of hospitalized is about 15%. The deaths from COVID-19 among rheumatic patients are 378 or 8.6%, which is almost three times higher than the mortality in the general population.

Coagulopathies and hyperinflammation are common in COVID-19 patients, with DIC syndrome and pulmonary thrombotic microangiopathy being the most common [37]. Some autoimmune rheumatic diseases, such as systemic lupus erythematosus (SLE) and Style's disease in adults, are characterized by systemic hyperinflammation, presented as macrophage activation syndrome (MAS) [38, 39]. MAS syndrome is a subtype of hemaphagocytic lymphohistocytosis (HLH), which is characterized by hyperinflammation that can be induced by COVID-19 [40].

To date, there is insufficient evidence that rheumatic diseases are characterized by a lower incidence of COVID-19, but are characterized by higher mortality than the general population. A study of 600 rheumatic patients who underwent COVID19 examined the effect of age, gender, comorbidities, and concomitant therapy on the severity of COVID-19 [41]. There is no increased risk of hospitalization

Fig. 2. This graph visualizes data from 600 patients with rheumatic diseases recorded in the COVID-19 Global Rheumatology Alliance international physician registry, reported by Gianfrancesco et al.

among patients undergoing conventional synthetic, biological or targeted-synthetic therapy. Significantly more severe COVID-19 has been reported in patients over 65 years of age, as well as those with diabetes, lung and vascular disease [41].

Patients with autoimmune rheumatic diseases are of special interest to science at the time of the epidemic, not only because of immune disorders, but also because of the fact that many conduct immunosuppressive therapy. Traditionally, these patients are at increased risk of infection, and the question remains whether they are exposed to a higher risk of COVID-19. Recent studies have found that uncontrolled disease and high disease activity are emerging as independent risk factors for severe disease [42, 43]. For example, in patients with rheumatoid arthritis, elevated DAS-28 values are associated with a 25% higher risk of hospitalization infections [44]. In patients with systemic lupus erythematosus and values of the disease activity index SLEDAI > 4 is associated with a 71% higher risk of infections [45].

At present, the world's scientific experience with SARS-CoV-2 is only about one year. Undoubtedly, there are many unknowns about both the spread of the virus and the treatment of COVID-19. The pathogenetic mechanisms of the disease as well as the factors contributing to its severity in some people are not fully understood.

Also, a number of questions are raised in relation to the treatment of autoimmune rheumatic diseases. At present, according to national and international recommendations for the treatment of rheumatic diseases in a pandemic with SARS-CoV-2, discontinuation of prescribed therapy is not recommended. In itself, exacerbation of autoimmune disease activity may be a risk factor for COVID-19.

The issue of vaccination is becoming more and more topical. It is the development of an effective and safe vaccine, as well as the availability of antiviral therapy, that are at the heart of overcoming the SARS-CoV-2 pandemic. Currently, most available vaccines target the production of antibodies against the S1 subunit of the spike protein, thereby targeting the attachment of the virus to the host cell. The mechanisms of invasion of the new coronavirus and the proportion of antibodies that are neutralizing are not fully understood. Cellular immunity plays a major role in antiviral mechanisms. Undoubtedly, the benefits to both society and rheumatic patients outweigh the risks. There are many unknowns for COVID-19 and SARS-CoV-2 vaccines, and the scientific community does not have sufficient data on vaccine side effects.

CONCLUSION

Despite the accumulated knowledge and experience so far, many questions still remain unclear. The developed algorithms and recommendations are constantly improved in order to refine the approach and provide the best care for the rheumatic patients in a pandemic with SARS-CoV-2.

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