Connections between COVID-19 and Autoimmune Diseases

Subjects: Infectious Diseases

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Autoimmune diseases and SARS-CoV-2 infections are intertwined in several ways. Both conditions lead to immune-mediated tissue damage, the immune response is accompanied by the increased secretion of inflammatory cytokines and both conditions can be treated using immunomodulatory drugs. Patients with certain autoimmune diseases, such as systemic lupus erythematosus, rheumatoid arthritis, type 1 diabetes, cardiac sarcoidosis, idiopathic pulmonary fibrosis, autoimmune hepatitis, multiple sclerosis and others, are more susceptible to SARS-CoV-2 infection, either because of the active autoimmune disease or because of the medications used to treat it. Conversely, SARS-CoV-2 infection can also cause certain autoimmune diseases.

Keywords: COVID-19 ; SARS-CoV-2 ; autoimmune diseases ; immune response

1. Introduction

SARS-CoV-2 is a novel coronavirus (CoV) that causes pandemic respiratory infectious disease COVID-19 with a fatality rate of approximately 2% [1][2][3]. The disease first emerged in December 2019 in Wuhan, China, and was officially declared a pandemic by the World Health Organisation (WHO) on 11 March 2020. The number of deaths due to COVID-19 is estimated at more than 6.4 million [4][5][6]. SARS-CoV-2 is a positive-polar single-stranded RNA (ssRNA) virus belonging to the genus Betacoronavirus group 2B. Genomic analyses have shown that it has 79.6% genomic sequence identity to SARS-CoV, which caused the outbreak of severe acute respiratory syndrome (SARS) in 2002, and 50% sequence homology to MERS-CoV, which caused the Middle East respiratory syndrome (MERS) epidemic in 2012–2013 [3][7][8]. The virus has four structural proteins: a spike protein (protein S), an envelope protein (E), a membrane protein (M) and a nucleocapsid protein (N). Protein S, with its receptor binding domain (RBD), plays a key role in infection. The target of the virus has been identified as the lung epithelium. The receptor binding domain (RBD), located in the S1 subunit of protein S, allows viral entry into host cells via the angiotensin-converting enzyme 2 (ACE2) receptor [3][4]. The S1/S2 polybasic cleavage site, which is proteolytically cleaved by the cellular cathepsin L and the transmembrane protease serine 2 (TMPRSS2) protease, is also important for infection [7]. The latter facilitates virus entry at the plasma membrane surface, whereas the lysosomal cysteine protease cathepsin L facilitates virus entry into cells lacking TMPRSS2 by activating protein S in endosomes [7][9][10]. SARS-CoV-2 is transmitted directly by respiratory droplets, as evidenced by the productive replication of SARS-CoV-2 in the upper and lower respiratory tract and by the many cases of human-to-human transmission of the virus during close contact with active coughing [7]. The virus passes through the nasal and laryngeal mucosa and, after binding to airway epithelial cells, enters the alveolar epithelial cells in the lung. From there, it can enter the peripheral blood and infect cells of tissues expressing the ACE2 protein, such as the heart, kidneys, gastrointestinal tract and brain [8][11]. The usual clinical manifestation of the virus is fever, fatigue, dry cough, headache, dyspnoea and sore throat. Olfactory and taste disturbances may also occur. Highly pathogenic CoV causes severe influenza-like symptoms that can progress to acute respiratory distress, pneumonia, renal failure or even death [4][7][12]. In most people, signs of infection appear after an incubation period of 1 to 14 days (most commonly around 5 days), and dyspnoea and pneumonia develop within eight days of onset of illness. All age groups are susceptible to SARS-CoV-2 infection, but the clinical picture varies according to age. Those aged 60 years and over are more likely to develop severe respiratory disease resulting in hospitalisation or, in severe cases, death, while most young people have mild or even asymptomatic symptoms [8]. The WHO reports that 80% of infections are mild to moderate and 13.1% develop severe disease. In 6.1% of those infected, critically severe disease requiring intensive treatment may develop [3]. Risk factors for the development of a more severe course include age over 60 years, high blood pressure, obesity, cardiovascular disease, diabetes mellitus, pregnancy, underlying lung disease and relative immunodeficiency [3][13]. Some people may develop long-lasting effects of infection, known as long COVID, after infection with SARS-CoV-2. This is defined by signs and symptoms that develop during or after infection that are consistent with COVID-19, last more than 12 weeks and cannot be explained by an alternative diagnosis. They are usually manifested by clusters of symptoms that often overlap, can fluctuate and

change over time and can affect any system in the body. Although long COVID often develops in people who have had a severe form of COVID-19, the condition can develop in anyone who has been infected with SARS-CoV-2 and especially in those who are being treated for various autoimmune diseases [14][15].

The immune system protects the body from foreign bodies, viruses, microbes and from infected or tumour cells. To function normally, the immune system must be able to distinguish between foreign bodies and the body's own antigens [16]. Autoimmunity is an immune response against the body's own antigens. Autoimmune disease occurs when tolerance to self-antigens breaks down. Antibodies that attack the body's own cells are called autoantibodies and the body consequently starts to produce antibodies against its own cells. The immune system works in the same way in autoimmune diseases as it does in defence against foreign bodies. Autoimmune diseases are caused by a disturbance in immune regulation. The disruption is caused by changes in the interaction between B and T lymphocytes and antigen-presenting cells (APCs). Antibodies that bind to self-antigens are produced. This results in immune complexes that activate complement or T lymphocytes that mature into cytotoxic lymphocytes, macrophages or natural killer (NK) cells. As a consequence, lytic mechanisms are triggered that are characteristic of complement activation or cell-mediated immune responses. This leads to tissue damage and inflammation [17][18][19]. Autoimmune diseases are influenced by both one's own genes and the environment. Genes can directly affect the cells of the immune system by altering autoreactivity. Changes in tissue function are manifested as altered lymphocyte and immune function. Environmental factors include the products of microorganisms (e.g., bacterial DNA and viruses). These factors can enhance the immune response to antigens and thus stimulate the natural immune system, thereby preventing the destruction of foreign bodies [16][20]. There are two broad groups of autoimmune diseases: organ-specific and systemic autoimmune diseases. In organ-specific autoimmune diseases, individual organs are affected, whereas in systemic autoimmune diseases, it is mainly organ-nonspecific antigens that are attacked (consequently, multiple organs are affected). These are either found in the bloodstream (e.g., rheumatoid factors) or are components of cells (e.g., anti-DNA antibodies) [17]. Each disease is characterised by unique antibodies that detect and target the antigens. Some of these antigens are located on a single organ, causing an organ-specific autoimmune disease, while others are located on multiple organs, causing a systemic autoimmune disease. Some of the more common organ-specific autoimmune diseases are as follows: autoimmune thyroid disease, type 1 diabetes, psoriasis, multiple sclerosis and Guillain–Barré syndrome. Common systemic autoimmune diseases include systemic lupus erythematosus, rheumatoid arthritis, chronic inflammatory bowel disease, Sjögren's syndrome and antiphospholipid syndrome [21][22].

2. Connections between COVID-19 and Autoimmune Diseases

There are several links between COVID-19 and autoimmune diseases. In both diseases, chronic inflammation with immune-mediated tissue damage is at the core [4][23]. In autoimmune diseases, tissue damage occurs due to sustained inflammatory reactions resulting from loss of immune tolerance due to immune dysfunction. This leads to damage and malfunction of various organs. As SARS-CoV-2 infection triggers immune reactions in the host, such immune-mediated damage also occurs in severe COVID-19 [19][24].

The excessive release of inflammatory cytokines and chemokines is a feature of both SARS-CoV-2 infection and autoimmune diseases, both of which can cause severe damage to various organs. Increased levels of interleukin-1 (IL-1), interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-8 (IL-8), interleukin-10 (IL-10), interleukin-17 (IL-17), interleukin-18 (IL-18), CXC chemokine ligand 10 (CXCL10) and CXC chemokine ligand 2 (CCL2) have been detected in SARS-CoV-2 infections. The level of expression of certain cytokines and the degree of cytokine imbalance influence the severity and outcome of the disease. Similar to autoimmune diseases, damage-associated molecular patterns (DAMPs), i.e., molecules released from damaged or dead cells as a result of infection or injury, can also worsen the course of infection and disease outcome [4][5][23][24].

In patients with COVID-19, the researchers confirmed extrafollicular B-cell activation and neutrophilia, as well as excessive macrophage activation resulting from cytokine storm. This is also characteristic of people with autoimmune diseases. This inflammatory state leads to the production of excessive inflammatory cytokines, the polarisation of activated macrophages towards an M1 inflammatory phenotype and cytotoxic dysfunction, which can ultimately lead to complications and a severe outcome of COVID-19. The activation of neutrophil granulocytes and the production of neutrophil extracellular traps (NETosis) play an important pathogenic role in COVID-19. Increased serum levels of neutrophil extracellular traps are also present in some autoimmune diseases, such as antiphospholipid syndrome [4][5][23][25]. Another important similarity between COVID-19 and autoimmune diseases is the use of immunomodulatory drugs and

biologic agents targeting inflammatory cytokines. Thus, corticosteroids, Janus kinase (JAK) inhibitors, IL-1 blockers and IL-6 receptor antagonists have been used to treat some severe forms of COVID-19 [4][5][12][23][26].

References

1. Deora, H.; Dange, P.; Patel, K.; Shashidhar, A.; Tyagi, G.; Pruthi, N.; Arivazhagan, A.; Shukla, D.; Dwarakanath, S. Management of Neurosurgical Cases in a Tertiary Care Referral Hospital During the COVID-19 Pandemic: Lessons from a Middle-Income Country. World Neurosurg. 2021, 148, e197–e208.
2. Brüssow, H. Immunology of COVID-19. Environ. Microbiol. 2020, 22, 4895–4908.
3. Adil, M.T.; Rahman, R.; Whitelaw, D.; Jain, V.; Al-Taan, O.; Rashid, F.; Munasinghe, A.; Jambulingam, P. SARS-CoV-2 and the pandemic of COVID-19. Postgrad. Med. J. 2021, 97, 110–116.
4. Liu, Y.; Sawalha, A.H.; Lu, Q. COVID-19 and autoimmune diseases. Curr. Opin. Rheumatol. 2021, 33, 155–162.
5. Lakota, K.; Perdan-Pirkmajer, K.; Hočevar, A.; Sodin-Semrl, S.; Rotar, Ž.; Čučnik, S.; Žigon, P. COVID-19 in Association With Development, Course, and Treatment of Systemic Autoimmune Rheumatic Diseases. Front. Immunol. 2021, 11, 611318.
6. Velnar, T.; Bosnjak, R. Management of neurosurgical patients during coronavirus disease 2019 pandemics: The Ljubljana, Slovenia experience. World J. Clin. Cases 2022, 10, 4726–4736.
7. Harrison, A.G.; Lin, T.; Wang, P. Mechanisms of SARS-CoV-2 Transmission and Pathogenesis. Trends Immunol. 2020, 41, 1100–1115.
8. Hu, B.; Guo, H.; Zhou, P.; Shi, Z.L. Characteristics of SARS-CoV-2 and COVID-19. Nat. Rev. Microbiol. 2021, 19, 141–154.
9. Zhao, M.M.; Yang, W.L.; Yang, F.Y.; Zhang, L.; Huang, W.J.; Hou, W.; Fan, C.F.; Jin, R.H.; Feng, Y.M.; Wang, Y.C.; et al. Cathepsin L plays a key role in SARS-CoV-2 infection in humans and humanized mice and is a promising target for new drug development. Signal Transduct. Target. Ther. 2021, 6, 134.
10. Padmanabhan, P.; Desikan, R.; Dixit, N.M. Targeting TMPRSS2 and Cathepsin B/L together may be synergistic against SARS-CoV-2 infection. PLoS Comput. Biol. 2020, 16, e1008461.
11. Sanyal, S. How SARS-CoV-2 (COVID-19) spreads within infected hosts—What we know so far. Emerg. Top. Life Sci. 2020, 4, 371–378.
12. Grange, L.; Guilpain, P.; Truchetet, M.-E.; Cracowski, J.-L. Challenges of autoimmune rheumatic disease treatment during the COVID-19 pandemic: A review. Therapies 2020, 75, 335–342.
13. Saini, L.; Krishna, D.; Tiwari, S.; Goyal, J.P.; Kumar, P.; Khera, D.; Choudhary, B.; Didel, S.; Gadepalli, R.; Singh, K. Post-COVID-19 Immune-Mediated Neurological Complications in Children: An Ambispective Study. Pediatr. Neurol. 2022, 136, 20–27.
14. Pires, R.E.; Reis, I.G.N.; Waldolato, G.S.; Pires, D.D.; Bidolegui, F.; Giordano, V. What Do We Need to Know About Musculoskeletal Manifestations of COVID-19?: A Systematic Review. JBJS Rev. 2022, 10, e22.00013.
15. Russell, D.; Spence, N.J.; Chase, J.-A.D.; Schwartz, T.; Tumminello, C.M.; Bouldin, E. Support amid uncertainty: Long COVID illness experiences and the role of online communities. SSM-Qual. Res. Health 2022, 2, 100177.
16. Paterson, C.; Davis, D.; Roche, M.; Bissett, B.; Roberts, C.; Turner, M.; Baldock, E.; Mitchell, I. What are the long-term holistic health consequences of COVID-19 among survivors? An umbrella systematic review. J. Med. Virol. 2022, 94, 5653–5668.
17. Kraft, H.; Weiss, F. Pandemic portfolio choice. Eur. J. Oper. Res. 2023, 305, 451–462.
18. Capone, F.; Rossi, M.; Cruciani, A.; Motolese, F.; Pilato, F.; Di Lazzaro, V. Safety, immunogenicity, efficacy, and acceptability of COVID-19 vaccination in people with multiple sclerosis: A narrative review. Neural Regen. Res. 2023, 18, 284.
19. Lorenz, H.M.; Herrmann, M.; Kalden, J.R. The pathogenesis of autoimmune diseases. Scand. J. Clin. Lab. Investig. Suppl. 2001, 235, 16–26.
20. Wang, L.; Wang, F.-S.; Gershwin, M.E. Human autoimmune diseases: A comprehensive update. J. Intern. Med. 2015, 278, 369–395.
21. Wu, X.; Wang, L.; Shen, L.; Tang, K. Response of COVID-19 vaccination in multiple sclerosis patients following disease-modifying therapies: A meta-analysis. eBioMedicine 2022, 81, 104102.

22. Lehuen, A.; Marshak-Rothstein, A. Organ-specific and systemic autoimmune diseases. Curr. Opin. Immunol. 2013, 25, 667–669.
23. Seissler, J.; Scherbaum, W.A. Are we ready to predict and prevent endocrine/organ specific autoimmune diseases? Spr inger Semin. Immunopathol. 2002, 24, 273–295.
24. Dorward, D.A.; Russell, C.D.; Um, I.H.; Elshani, M.; Armstrong, S.D.; Penrice-Randal, R.; Millar, T.; Lerpiniere, C.E.B.; Tagliavini, G.; Hartley, C.S.; et al. Tissue-Specific Immunopathology in Fatal COVID-19. Am. J. Respir. Crit. Care Med. 2021, 203, 192–201.
25. Zuo, Y.; Yalavarthi, S.; Gockman, K.; Madison, J.A.; Gudjonsson, J.E.; Kahlenberg, J.M.; McCune, W.J.; Bockenstedt, P.L.; Karp, D.R.; Knight, J.S. Anti–Neutrophil Extracellular Trap Antibodies and Impaired Neutrophil Extracellular Trap D egradation in Antiphospholipid Syndrome. Arthritis Rheumatol. 2020, 72, 2130–2135.
26. Yalavarthi, S.; Gould, T.J.; Rao, A.N.; Mazza, L.F.; Morris, A.E.; Núñez-Álvarez, C.; Hernández-Ramírez, D.; Bockenste dt, P.L.; Liaw, P.C.; Cabral, A.R.; et al. Release of Neutrophil Extracellular Traps by Neutrophils Stimulated With Antipho spholipid Antibodies: A Newly Identified Mechanism of Thrombosis in the Antiphospholipid Syndrome. Arthritis Rheumat ol. 2015, 67, 2990–3003.
