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REVIEW

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Autoimmune complications of COVID-19

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Abstract

Coronavirus disease 2019 (COVID-19) is still propagating a year after the start of the pandemic. Besides the complications patients face during the COVID-19 disease period, there is an accumulating body of evidence concerning the late-onset complications of COVID-19, of which autoimmune manifestations have attracted remarkable attention from the first months of the pandemic. Autoimmune hemolytic anemia, immune thrombocytopenic purpura, autoimmune thyroid diseases, Kawasaki disease, Guillain-Barre syndrome, and the detection of autoantibodies are the cues to the discovery of the potential of COVID-19 in inducing autoimmunity. Clarification of the pathophysiology of COVID-19 injuries to the host, whether it is direct viral injury or autoimmunity, could help to develop appropriate treatment.

KEYWORDS

autoantibody, autoimmunity, COVID-19, cytopenia, SARS-CoV-2

1 | INTRODUCTION

The world has witnessed the emergence of the rapidly growing pandemic of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) since December 2019. Affecting almost all countries, areas, and territories with more than 195 million confirmed cases and over 4 million death worldwide at the time of this writing—July 26, 2021,[1] this newly emerged virus has become the main health concern since late 2019.[2] Molecular investigations have been conducted to provide a more detailed understanding of the SARS-CoV-2 viral structure that might help to design or repurpose potential drugs or vaccines;[3–6] while laboratory and clinical surveys aim to discover the different clinical manifestations of this infection and its association with other diseases and health complications. For instance, according to previous reports on autoimmune manifestations and autoimmune-related markers in coronavirus disease 2019 (COVID-19) patients, a growing body of research has been devoted to the exploration of the association between COVID-19 infection and autoimmune conditions. Acute hemolytic anemia, macrophage activating syndrome, Kawasaki-like disease, Guillain-Barre syndrome (GBS), Miller Fisher syndrome (MFS), autoimmune thrombotic thrombocytopenic purpura, autoimmune skin manifestations, and detection of autoantibodies are some of the pieces of evidence pointing to the potential interconnection between autoimmunity and COVID-19.[7–11] As COVID-19 could be considered as a predisposing factor for auto-reactivity and is involved in mechanisms contribute to the initiation of autoimmunity, investigating the mutual association of autoimmunity and COVID-19 is of interest. Meanwhile, outcomes of explorations about the molecular mechanisms and related pathways involved in the association of autoimmunity and COVID-19 might be beneficial for accelerating the process of designing the treatment strategy, if translated to clinical utilization.[12]

2 | INFECTION AND AUTOIMMUNITY

Infections have been known as the most important environmental trigger in the complex pathophysiology of autoimmune diseases. Different mechanisms are hypothesized to explain how infections might provoke autoimmune reactions. Epitope spreading, bystander activation, cross-reaction or molecular mimicry, and presentation of cryptic antigens are the suggested mechanisms.[13] For instance, type 1 diabetes mellitus (T1DM) as one of the most prevalent autoimmune diseases has been suggested to be associated with coxsackievirus,[14] cytomegalovirus (CMV),[15] and enteroviruses.[16] Different types of viral infections such as hepatitis C virus (HCV),[17] CMV,[18] dengue virus,[19] and parvovirus B19[20,21] have been postulated to be associated with systemic lupus erythematosus (SLE) that represent a wide

TABLE 1 Autoimmune conditions associated with viral infections

Associated autoimmunity	Virus	References
T1DM	Coxsackievirus	Eizirik and Op de Beeck[14]
	CMV	Pak et al.[15]
	Enteroviruses	Stene and Rewers[16]
	Rotavirus	Gómez-Rial et al.[27]
SLE	HCV	Stölzel et al.[28]
	CMV	Chen et al.[18]
	Dengue virus	Rajadhyaksha and Mehra[19]
	Parvovirus B19	Aslanidis et al.[20] and Chabert and Kallel[21]
MS	EBV	Guan et al.[22]
	Measles virus	Tucker and Paskauskas[23]
	VZV	Sotelo et al.[24]
	CMV	Thakolwiboon et al.[25,26]
	Theiler's virus	Miller et al.[29]
ME/CFS	HHV-6	Ablashi et al.[30]
	EBV	Holmes et al.[31]
	Enteroviruses	McGarry et al.[32]
	Lentiviruses	Holmes et al.[33]
	CMV	Martin[34]
CD	Rotavirus	Gómez-Rial et al.[27]
AIH	EBV	Cabibi[35]
	HCV	Tampaki and Paskauskas[36]
MG	WNV	McBride et al.[37]
	JEV	He et al.[38]
RA	CMV	Pera et al.[39]
	EBV	Dostál et al.[40]
GBS	Zika virus	Smatti et al.[41]
	EBV	Kuwabara[42]
	CMV	Kuwabara[42]
	Measles virus	Esposito and Longo[43]
	Enterovirus D68	Esposito and Longo[43]
	Influenza A	Esposito and Longo[42]
KD	Adenoviruses	Chang et al.[44]
	Enteroviruses	Chang et al.[44]
	Rhinoviruses	Chang et al.[44]

Abbreviations: AIH, autoimmune hepatitis; CD, celiac disease; CMV, cytomegalovirus; EBV, Epstein-Barr virus; GBS, Guillain-Barre syndrome; HCV, hepatitis C virus; HHV, human herpesvirus; JEV, Japanese encephalitis virus; KD, Kawasaki disease; ME/CFS, myalgic encephalomyelitis/chronic fatigue syndrome; MG, myasthenia gravis; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1DM, type 1 diabetes mellitus; VZV, varicella-zoster virus; WNV, West Nile virus.

variety of autoimmune manifestations. Furthermore, multiple sclerosis (MS) has been found to be associated with Epstein-Barr virus (EBV),[22] measles virus,[23] Varicella-zoster virus,[24] and CMV[25,26] (Table 1). The aforementioned examples support the role of viral infections in the initiation of autoimmune diseases particularly in individuals with genetic susceptibility.

Considering the current challenges of the COVID-19 pandemic regarding the discovery of proper vaccine or treatment, mental and physical health complications of social isolation, and healthcare expenses, the huge burden of this pandemic is evident.[45] On the other hand, autoimmune diseases induce a noticeable burden to society, individuals, and the healthcare system as well, as these are prevalent chronic conditions with no definite treatment up to date.[46,47] Taken together, the concomitance of COVID-19 infection and autoimmune diseases potentially induce a huger burden worldwide, as either the occurrence of COVID-19 infection in patients with pre-existing autoimmune diseases or the initiation of autoimmune manifestations in individuals with COVID-19 are associated with different complications.

3 | AUTOIMMUNE COMPLICATIONS OF COVID-19 INFECTION

From the start of the outbreak, several reports have appeared on the autoimmune manifestations and autoimmune sequelae of COVID-19 infection. Taking into consideration that viruses can induce type II and IV hypersensitivity reactions besides their specific cytopathic effect, COVID-19-mediated autoimmunity might be rationalized.[48] Production of autoantibodies following a viral infection that potentially leads to tissue injury (cross-reaction) is the suggested mechanism for viral-induced autoimmunity based on the concept of type II hypersensitivity.[49] Regarding type IV hypersensitivity, it is suggested that activated T cells against the virus might damage the self-tissues by conducting an inflammatory environment or directly attacking the cells. Furthermore, there are many theories explaining how SARS-CoV-2 mediates a hyperinflammatory state that results in autoimmune reactions; for instance, vascular injury due to immune-complex depositions and antibody-dependent enhancement (ADE) with immune complexes formed by IgG that potentially boosts viral replication in Fc-receptor expressing cells.[50] The observation of ADE by anti-spike protein antibody of severe acute respiratory syndrome coronavirus (SARS-CoV) further supports the possible role of ADE in autoimmunity mediated by COVID-19.

Clinical and laboratory findings indicate the hyperactivity of the immune system in COVID-19 cases. A study has compared the concentration of inflammatory markers in intensive care unit (ICU) admitted patients versus non-ICU patients.[51] Interleukin-2 (IL-2), IL-7, IL-10, tumor necrosis factor-α (TNF-α), GCSF, MIP-1A, IP-10, MCP-1, IFN-γ, and IL-1β were detected at higher levels in the blood samples of ICU patients, of which the last four mentioned immune mediators potentially initiate cytokine storm by stimulating the T helper 1 (Th1) immune response.[51] This might

be correlated with the disease severity of ICU-admitted patients. Besides, immune dysregulation was observed in COVID-19 patients particularly in severe cases. Qin *et al*. have tested 452 cases of COVID-19 and recorded the immunological findings from testing their blood samples.[52] They reported a higher elevated level of IL-2R, IL-6, IL-8, IL-10, and TNF-α in severe cases compared to non-severe cases.[52] Moreover, although the total count of B cells, natural killer (NK) cells, and T cells were declined significantly, especially in severe cases, it was observed that T cells were influenced more significantly than others were. $CD3^+CD4^+$T helper cells were reduced as well as the $CD3^+CD8^+$ suppressor T cells, whereas $CD3^+CD8^+CD28^+$ suppressor cells were much remarkably lower in severe cases but the decrease in $CD4^+CD8^+$HLA-DR^+ suppressor T cells level was not reported to be more significant in severe cases than in non-severe patients.[52] Furthermore, naïve T cells and induced T regulatory (iTreg) cells ($CD45^+CD3^+CD4^+CD25^+CD127low^+$) that are in charge of impeding the hyperinflammation and autoimmune reactions, represented a more prominent decrease in patients with severe COVID-19.[52] Considering all the aforementioned findings regarding the immune dysregulation evidence in infected patients with COVID-19, postulating an autoimmunity process in the course of COVID-19 infection is of interest.

The described immune dysregulation along with the overproduction of cytokines that potentially leads to self-tissue damage is known as secondary hemophagocytic lymphohistiocytosis (HLH) that could usually appear following viral infections.[53,54] The secondary HLH is documented in SARS-CoV patients as well.[55]

Although it has been presumed from the early time of the pandemic that COVID-19 does not severely affect children and the infection is mostly asymptomatic,[56,57] observation of hyperinflammatory symptoms that potentially could conduct a favorable state for the initiation of autoimmune reactions was one of the important clues to the association of autoimmunity with COVID-19. Since late April 2020, the first reports of a multisystem inflammatory syndrome in children (MIS-C) related to COVID-19, in which its manifestations mimic Kawasaki disease, acquired considerable attention. Gastrointestinal, cardiovascular, hematologic, mucocutaneous, and respiratory involvement was of the most common findings in COVID-19 pediatric patients presented with MIS-C, respectively.[58] These findings are in line with the obtained results from the same studies.[57,59–62] As the antibody titer against COVID-19 was positive in the mentioned patients, it is fair to attribute the hyperinflammatory environment to the COVID-19-mediated cytokine storm than the direct viral injury to the host's cells. A hyperinflammatory environment may lead to the activation of immune components that could result in autoimmune reactions.[63] MIS-C demonstrates both type II and type IV hypersensitivity characteristics.[64] The delay between the emergence of autoinflammatory syndromes and COVID-19 spread peaks might strengthen the possibility of virus-induced immune-mediated mechanisms underlying the reported clinical manifestations.[58] MIS-C could occur during the whole course of the COVID-19 infection, while autoimmune manifestations in infected adults are often observed in the early active phase of the disease.[8,65–67]

Different reports regarding the autoimmune associations of COVID-19 infection have gradually started to emerge. For instance, the first documented autoimmune reaction to the human nervous system was a case of a patient who developed weakness of her lower limbs that progressed to upper limbs within three days.[68] This patient's GBS diagnosis was confirmed by CSF test and electromyography. Meanwhile, she tested positive for COVID-19 while having GBS symptoms.[68] Incidence of different peripheral nervous involvement stages in COVID-19 infected individuals, known as MFS, acute motor axonal neuropathy, and acute inflammatory demyelinating polyneuropathy has been reported through more studies.[66,69–74] Existing reports on the neurologic autoimmune manifestations following infection with other coronaviruses such as SARS-CoV and Middle East respiratory syndrome coronavirus, further support the notion that COVID-19 might be capable of inducing autoimmune reactions against the nervous system.[75,76]

Immune thrombocytopenic purpura (ITP) is defined as immunological destruction of platelets that result in a low number of circulating platelets. It has been reported in association with viral infections such as human immunodeficiency virus and HCV that are the well-described ones.[77] Thrombocytopenia in a moderate form is reported in about 36% of admitted COVID-19 patients.[78] However, a number of reports are indicative of the occurrence of thrombocytopenia in COVID-19 patients.[7,67,79–81] Meanwhile, a meta-analysis suggested that thrombocytopenia is more pronounced in patients with a severe form of COVID-19 infection.[82] Similar to COVID-19, SARS-CoV has been reported to be associated with thrombocytopenia that is attributed to direct viral injury to endothelium and the damage from mechanical ventilation[83] potentially stimulating platelet activation and aggregation in the lungs, which in turn decline the number of platelets. However, the mechanism of ITP in COVID-19 remains to be explored. A case of Evans syndrome that is the concurrent incidence of ITP and hemolytic anemia is reported in a patient with COVID-19. Considering other COVID-19 cases that had developed hemolytic anemia,[9,65,84,85] besides the mentioned cases of ITP patients, the incidence of Evans syndrome could be the result of autoimmune reactions following COVID-19 infection.

There are several reports concerning the autoimmune endocrine pathologies following COVID-19 infection, for instance, autoimmune thyroid diseases.[86–88] Lui et al. in a recent cohort studied the thyroid dysfunctions in admitted COVID-19 patients. They observed that incidence of thyroiditis during the convalescence period was rare; however, imbalances in the thyroid function tests and the detection of anti-thyroid antibodies in these patients highlighted the importance of thyroid screening tests in patients who have a history of COVID-19.[86] Nevertheless, patients who had detectably altered thyroid function at admission recovered through the convalescence period.[86] An overview of the recent reports regarding the autoimmune complications of COVID-19 is provided in Table 2.

TABLE 2 Reports of the most prevalent autoimmune conditions associated with COVID-19

Autoimmune disease	Country	Study design	Number of patients	Reference
Guillain-Barre syndrome	Italy	Case series	2	Assini et al.[89]
	France	Case series	2	Bigaut et al.[90]
	United States	Case series	2	Chan et al.[91]
	Iran	Case series	2	Ebrahimzadeh et al.[92]
	Brazil	Cohort	6	Espindola et al.[93]
	Italy	Cohort	30	Filosto et al.[94]
	Italy	Cohort	17	Filosto et al.[95]
	Spain	Cohort	11	Filosto et al.[96]
	Italy	Case series	6	Garnero et al.[97]
	India	Case series	2	Goel et al.[98]
	Belgium	Cohort	3	Goel et al.[99]
	Spain	Case series	2	Gutiérrez-Ortiz et al.[74]
	UK	Cohort	25	Keddie et al.[100]
	France	Case series	2	Cleret de Langavant et al.[101]
	Switzerland	Case series	3	Lascano et al.[102]
	Italy	Case series	5	Manganotti et al.[103]
	France	Cohort	15	Meppiel et al.[104]
	India	Case series	4	Nanda et al.[105]
	UK	Case series	3	Paterson et al.[106]
	Iran	Case series	2	Paybast et al.[107]
	Italy	Case series	5	Toscano et al.[66]
Immune thrombocytopenic purpura	UK	Case series	3	Ahmed et al.[108]
	The Netherlands	Case series	3	Bomhof et al.[109]
	United States	Case series	2	Guirguis et al.[110]
	France	Case series	3	Lorenzo-Villalba et al.[111]
	France	Case series	14	Mahévas et al.[112]
	Italy	Case series	3	Pascolini et al.[113]
	Portugal	Case series	2	Pedroso et al.[114]
	France	Case series	3	Revuz et al.[115]
	China/France	Case series	2	Yang et al.[116]
	Turkey	Case series	2	Aydin and Demircan[117]
Autoimmune hemolytic anemia	France	Case series	2	Huscenot et al.[118]
	United States	Case series	2	Huscenot et al.[119]
	France	Case series	7	Lazarian et al.[120]
Kawasaki disease	Oman	Case series	6	Al Maskari et al.[121]
	France	Case series	35	Belhadjer et al.[62]
	United States	Cohort	99	Dufort et al.[122]
	United States	Cohort	186	Feldstein et al.[59]

(Continues)

TABLE 2 (Continued)

Autoimmune disease	Country	Study design	Number of patients	Reference
	Qatar	Case series	7	Hasan et al.[123]
	Romania	Case series	2	Ionescu et al.[124]
	Austria	Case series	8	Kurz and Gombala[125]
	Peru	Case series	10	Luna-Muñoz et al.[126]
	Iran	Case series	45	Mamishi et al.[127]
	France	Cohort	16	Pouletty et al.[128]
	UK	Cohort	15	Ramcharan et al.[129]
	UK	Case series	8	Riphagen et al.[61]
	France	Case series	21	Toubiana et al.[62]
	Italy	Case series	10	Verdoni et al.[59]
	Germany/Austria	Case series	3	Wehl et al.[131]
	UK	Case series	58	Whittaker et al.[131]
Autoimmune thyroid disease	China	Cohort	22	Lui et al.[86]
	Spain	Case series	2	Mateu-Salat et al.[132]
	China	Case series	28	Chen et al.[133]

Interestingly, different autoantibodies have been detected in COVID-19 patients. For instance, antinuclear antibodies (ANA), lupus anticoagulant, anti-β2glycoprotein 1, and an anticardiolipin antibody that could be the cause of thromboembolic events in COVID-19 patients.[11,134,135] Moreover, anti-Ro/SSA and autoantibody against type I IFN were reported detectable in COVID-19 patients.[135,136] In addition, existing documents regarding the autoimmune cutaneous manifestations of COVID-19 and the onset of Grave's disease after COVID-19 infections further support the possibility of COVID-19-mediated autoimmunity.

4 | CONCLUSION

Autoimmune diseases are chronic disabling conditions that negatively affect individuals, families, society, and the healthcare system. Besides this, pandemics are always associated with different concurrent complications and challenges, as well as potential sequelae that may emerge either early or late after the pandemics. According to the evidence of COVID-19-mediated autoimmunity, it might be fair to think of autoimmunity as a serious complication of COVID-19. Understanding the pathophysiology of autoimmune manifestations in COVID-19 patients might help further elucidating the mechanism of viral injury to the host's body, whether it is the direct viral injury or autoimmune reactivity, which in turn could lead to a better and more efficient design of a treatment strategy. On the other hand, presuming the reactivity of the immune system as a result of COVID-19 infection and considering the earlier experience of the delay between the surge in the number of MIS-C or Kawasaki-like disease and the spread peaks of COVID-19, a time gap is expectable between the COVID-19 pandemic and autoimmune presentations.[137] Hence, a more precise understanding of the involved mechanisms potentially helps to monitor and prevent the incidence or exacerbation of autoimmune manifestations.

CONFLICT OF INTERESTS

The authors declare that there are no conflict of interests.

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