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Autoimmune complications of COVID-19 and potential consequences for long-lasting disease syndromes

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ABSTRACT

The latest WHO report determined the increasing diversity within the CoV-2 omicron and its descendent lineages. Some heavily mutated offshoots of BA.5 and BA.2, such as BA.4.6, BF.7, BQ.1.1, and BA.2.75, are responsible for about 20% of infections and are spreading rapidly in multiple countries. It is a sign that Omicron subvariants are now developing a capacity to be more immune escaping and may contribute to a new wave of COVID-19. Covid-19 infections often induce many alterations in human physiological defense and the natural control systems, with exacerbated activation of the inflammatory and homeostatic response, as for any infectious diseases. Severe activation of the early phase of hemostatic components, often occurs, leading to thrombotic complications and often contributing to a lethal outcome selectively in certain populations. Development of autoimmune complications increases the disease burden and lowers its prognosis. While the true mechanism still remains unclear, it is believed to mainly be related to the host autoimmune responses as demonstrated, only in some patients suffering from the presence of autoantibodies that worsens the disease evolution. In fact in some studies the development of autoantibodies to angiotensin converting enzyme 2 (ACE2) was identified, and in other studies autoantibodies, thought to be targeting interferon or binding to annexin A1, or autoantibodies to phospholipids were seen. Moreover, the occurrence of autoimmune heparin induced thrombocytopenia has also been described in infected patients treated with heparin for controlling thrombogenicity. This commentary focuses on the presence of various autoantibodies reported so far in Covid-19 diseases, exploring their association with the disease course and the durability of some related symptoms. Attempts are also made to further analyze the potential mechanism of actions and link the presence of antibodies with pathological complications.

1. Introduction

These past years, the world is facing the Covid-19 pandemic and its many side effects on lock-down, economy impact, morbidity and mortality, especially in at risk people, with many associated or synergistic clinical complications, with lung and tissue damage, exacerbated inflammation, immuno-thrombosis leading to multiorgan failure and fatal outcome in some infected patients [1,2]. In addition, in a significant group of SARS-Cov-2 infected patients, long-lasting symptoms of fatigue and other health burdens are reported, following the acute phase disease, and recovery from its major health concerns [3–5]. These persistent pathological consequences are independent of disease severity, and patients' age, gender and health status [5,6]. Little is still known about factors which can favor or induce this long Covid-19 syndrome, although some characteristics have been elucidated recently, and involve the remanence of a strong inflammatory context [7]. We, and others, early suspected the possible involvement of autoimmune complications during the disease course [8–11].

Yet, generation of autoantibodies during infectious diseases has been reported in some cases, associated with many different causative pathogens, but mainly with cytomegalovirus, Epstein Barr virus and Human Immunodeficiency virus [12–15]. These induced autoantibodies are identified when they produce severe complications, which depend on the autoantigen target, their concentration, and their impact on physiological processes [16,17]. However, their prevalence is probably underestimated, as these autoantibodies are only investigated when severe and unusual complications occur in patients, often associated with unexpected laboratory results [18]. This, is for example, the case of autoantibodies to coagulation Protein S, which have been identified in rare patients who developed thrombotic events during or just after

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Table 1
Possible occurrence of some acquired autoantibodies in various clinical conditions et their pathological consequences (non-exhaustive); LA: lupus anticoagulant; DIC: disseminated intravascular coagulation; PF4: platelet factor 4; FV: factor V; FVIII: factor VIII.

Pathology	Possible autoantibodies	Main clinical impact
Viral infections, treatments with some drugs, malignancy	LA, Antiphospholipid Antibody, Anti-β2-GP1, Anti-Annexin V, Anti-prothrombin	Thrombosis Fœtal loss Skin necrosis
Varicella	Anti-Protein S	Thrombosis, mainly microvascular
Pharyngeal infection (adenovirus ?, others?)	Anti-Prothrombin, LA Anti Platelet Factor 4	Bleeding, bruise, « Apparent » coagulation factors deficiency Thrombocytopenia, Thrombosis (brain, unusual sites, etc.)
Malignancies	Anti-vWF, Anti-FVIII Anti-PF4, others	Bleeding Thrombocytopenia, Thrombosis
Fibrin glue (bovine thrombin)	Anti-thrombin	Thrombosis, DIC
Heparin therapy	Anti-PF4-heparin	Thrombocytopenia, thrombosis
Lymphoproliferative, others	Anti-FXIII, LA	Bleeding
Adenovirus vector vaccines	Anti-PF4	Unusual thrombosis, DIC
Second line antibiotics/antibioresistance	Anti-FV	Severe bleeding, Apparent coagulation Factors deficiency
Quinidine	Anti platelet (anti GPIIb-IIIa)	Thrombocytopenia, bleeding
Cytomeglovirus, Epstein Barr virus	Anti-Platelet antibodies	Thrombocytopenia, Bleeding
Hemophilia therapy	Anti-FVIII	Bleeding, Substitutive therapy resistance

varicella [19–23], but many other situations could be cited, and will be briefly discussed in the following paragraph.

The components not the body which are candidates to become autoantigens are blood or cell surface proteins which bind strongly to pathogens or to their metabolites, and are then involved in complexes targeted by the body's immune response [24]. Other reports have suggested that the immune system can contribute to regulate excess of inflammation by generating autoantibodies reactive with some inflammatory cytokines, as shown for Interleukine-8 (IL8) or other cytokines by Bendzen et al. [25–28]. These latter can be present in healthy individuals. In Covid-19, SARS-Cov-2 binds strongly to the Angiotensin-Converting-Enzyme 2 (ACE2) through the Receptor Binding domain (RBD) from its spike protein [29], and in severe cases a cytokine storm occurs and strongly worsens the disease course and its prognosis [30,31]. Autoimmune complications can contribute to worsen disease and to induce lasting symptoms with persistent inflammation [32,33]. When present, autoantibodies remain for weeks or months, and then they progressively decrease with time, when the autoantigen stimulus disappears. However, in a small subset of patients, these complications can switch to chronic autoimmune diseases [34,35]. This systematic review is focused on various autoimmune complications, which have been observed in Covid-19, their contribution to disease evolution, laboratory tools for their identification and quantitation, and their possible implication in long-lasting disease [36–40].

2. Association of autoantibodies with infectious diseases

Development of autoantibodies in many infectious diseases has been widely reported, with a high variety of pathogens, but these complications remain rare, at least for those characterized, and they are reported to affect a subgroup of infected individuals [41,42]. Actually, only some patients with symptomatic antibodies are currently diagnosed, when the target antigen is identified and clinical complications associated to the presence of these antibodies. This could, however, remain highly underdiagnosed as autoantibodies can remain asymptomatic, when their concentration is not high enough for being pathogenic, or because their binding to the target antigen is irrelevant. Interestingly, the Lupus Anticoagulant occurs, most often as transitory, as is much infectious pathology, suggesting a more extended implication of autoimmune processes [43,44]. Even if some autoantibodies develop more specifically in certain diseases, the causes which explain why only few individuals are affected remains highly problematic. This could result: i) from a specific presentation of the autoantigen exposing cryptic epitopes or a modified structure, ii) when this autoantigen forms complexes with a viral non-self-component, or its metabolites, iii) from some mimicry of viral proteins with self-components or, iv) from the involvement of self-components in pathogenic complexes, which then induces the spreading of the immune response (epitope spreading) [45–47]. The autoimmune complications described in infected patients can affect many different targets, especially those present in the blood. Epstein Barr or Cytomegalovirus infections can generate autoantibodies to platelets, which can provoke thrombocytopenia [48,49]. Adenovirus infections can induce autoantibodies to prothrombin, which are detected because they produce a strong Lupus Anticoagulant (LA) like activity, with an apparent decrease of Factors X, VIII, IX, X, XI and XII clotting activities, while antigenic concentrations remain normal [50–52]. Another striking case concerns autoantibodies to Protein S, which can develop in some patients with varicella, and are identified because thrombosis occurs and is associated with a decreased Protein S anticoagulant activity, occurring in patients not known before the infectious disease to carry any such deficiency [19–21]. Table 1 shows some of these antibodies reported in various clinical conditions, and their pathological effects. In all these contexts, autoimmune disease occurs within the infectious disease course, which demonstrates the

causative origin the complication, and autoantibodies tend to decrease and vanish months after their induction. This complication can then be classed as allo-immune. In some rare cases autoantibodies can become chronic, and last for a very long time with the symptomatic complications remaining [53,54]. Treatments used for treating autoimmune diseases target the symptoms to reduce their harmful effect, or they reduce the immune response as with corticoid therapy. In many cases of suspected autoimmune complications, only the Lupus Anticoagulant is detected during or after an infectious disease, and the target phospholipid cofactor protein is not always identified, although β2-Glyco-Protein 1 (β2GP1) or prothrombin are frequently involved [55,56]. Many other phospholipid binding proteins can also generate LA activities, like those targeted to Annexin V (A5) [57], Protein S or Factor XIII.

Clearly, the associations between some viral infectious diseases, such as Covid-19, and autoimmunity, are bidirectional, as if the pathogen itself or its metabolites, especially when complexed with self-proteins or the body's cells, generate autoantibodies through molecular mimicry or epitope spreading [45–47]. Conversely, patients with autoimmune diseases show a higher propensity for viral infections, resulting from the chronic inflammation and weakening of the body's defenses.

3. Other potential causes of autoantibodies generation

Any cause which leads to the introduction of a foreign component to the body has a potential capacity to induce autoantibodies, especially when it binds to cell receptors or to functional proteins, particularly those present in the blood circulation. The basic mechanism relies on the exposure of self-proteins in an unfolded way or an unusual presentation, unmasking cryptic epitopes, or on the extension of the immune response, first targeted to non-self-components, complexed with self-components, through epitope spreading. These conditions can also occur with some drug treatments, after insect, parasite or snake bites, or can be associated with malignancies and degenerative diseases which alter the cell origin presentation and can expose receptors or proteins in an unusual manner. The beneficial immune response to malignant cells can be deviated to healthy original cells, and this leads to development of an autoimmune response.

To illustrate this feature, we can cite: i) the generation of autoantibodies following tick bites [58], ii) those to Factor V, induced for example, by second line antibiotics to treat iatrogenic infections [59,60], iii) those induced by heparin therapy and platelet factor 4 (PF4) dependent, which can cause thrombocytopenia and thrombosis, iv) antibodies generated by treatments with a variety of other drugs [61–64], v) anti-PF4 autoantibodies developed in vaccine induced thrombotic thrombocytopenia, occurring in very rare patients vaccinated with adenovirus-vector vaccines against SARS-Cov-2 [65,66], vi) and autoimmune complications in cancer patients [67,68]. This list is obviously not exhaustive. In most cases, when the cause inducing autoimmunity is withdrawn, autoantibodies progressively decrease and disappear within few months, but the immune memory can remain activatable in case of a new exposure to the autoantigen, and generation of autoantibodies can therefore occur much faster [69]. The autoimmune complication is usually transitory, and patients fully return to a healthy state within few months. However, in some cases, autoimmune disorders can be persistent, with autoantibodies becoming chronic [70].

4. Pathogenicity of autoantibodies

Autoimmune complications are usually detected when clinical symptoms develop, and they are the result of the generation of autoantibodies targeted to body components. The target antigen is not always identified. Often, the reported autoantibody target concerns a side effect (like lupus anticoagulant) and not the exquisite autoantibody targeted structures, or the entire targeted cell or organ (anti-platelet, anti-endothelial cells, anti-kidney, etc.). A better understanding of the mechanisms involved requires the accurate identification of the autoantigen, and of the targeted epitopes, which have been described in many cases, but in many others still need to be identified [71,72].

Not all antibodies are pathogenic. They can be irrelevant, or remain asymptomatic. Harmful effects develop when antibodies react with proteins, impacting their function, or when they are targeted to cells or organ/tissues, where they activate the immune response and the complement pathways [73–75]. An autoimmune response more often develops to low or very low concentration proteins, although it can also be observed to proteins or biological structures present at high concentrations. Deleterious effects occur when antibodies block a key physiological function, like that of cytokines, growth factors, or other mediators, or when they activate, or destroy a cell line, like platelets or endothelial cells, or an organ. The pathogenicity of autoantibodies depends on the targeted autoantigen and specific epitopes, their concentration, and their affinity, which define their interference in physiological functions, or the destruction extent of the targeted cell line or organ. The higher is the autoantibody concentration and avidity, the stronger are the deleterious pathological effects, through the activation or destruction of the targeted cells or organs. The presence of risk factors can highly enhance the harmful effects of autoantibodies, especially when they favor thrombotic events: a preexisting imbalance of hemostasis leads to the development of thromboism in the presence of low autoimmune stimuli, which do not induce pathological impact in healthy individuals. This is, for example,the case of the association of LA with factor V Leiden or deficiencies of antithrombotic proteins, like Antithrombin, Protein C or Protein S, or a hypofibrinolytic state [76,77].

5. Pathological complications of autoantibodies

Pathological conditions resulting from autoantibodies are very heterogenous, and are associated with their autoantigen target, its physiological function and location, its binding onto cell surfaces, and its concentration. Deleterious effects are enhanced when targeted components, carrying a key biological activity, are present at low concentration, and bind onto cell surface receptors. The immune response is then targeted to these cells, which expose receptors or components able to interact with the autoantigen. Therefore, when autoantibodies bind directly or indirectly onto blood cells, they frequently can produce cell destruction, or activation, and they can generate thrombotic episodes. Activation of endothelial cells or platelets by autoantibodies, or their interference in antithrombotic processes is an important cause of thrombosis. When autoantibodies are targeted at hemostasis proteins in the blood, their effect depends on their interaction with physiological functions. Autoantibodies can reduce the activity of targeted antigens and induce bleeding when coagulation factors are concerned, like Factor V or Factor VIII, or thrombosis if they bind antithrombotic proteins, like Protein S. Another potential effect of autoantibodies concerns their binding to non-active epitopes on proteins, which reduces their half-life in the blood by accelerating their clearance.

Autoantibody-protein complexes can also interfere in physiological functions by binding to active biological surfaces inducing a steric hindrance which interferes with normal activities. Examples are those of autoantibodies to coagulation Protein S, Prothrombin, β2-GlycoProtein 1, Annexin V, all producing Lupus Anticoagulant activities [78,79], or to Thrombomodulin [80]. In other cases, antibodies can produce bleeding, especially when targeted to some platelet surface glycoproteins, inducing thrombocytopenia, or to clotting factors like Factor V, Factor VIII, Factor IX, von Willebrand Factor or Factor XIII [81–84].

When present, autoantibodies are extremely difficult to control. The first key action is to remove the cause producing autoimmunization, when possible. In heparin induced thrombocytopenia, stopping heparin has the double advantage of suppressing the immune stimulation and removing the target antigen which requires heparin Platelet Factor 4 [62]. But in the vast majority of autoimmune complications, suppressing the target autoantigen is not possible, and, when stimulated, autoantibody production lasts for a long time, even though it tends to decrease

with time. However, the half-life of antibodies, when B-cells are stimulated, is of several weeks or months, and their harmful consequences require appropriate management. Current treatments are symptomatic, to control and limit the major deleterious effects of autoantibodies, or they aim to reduce the autoantibody concentration, through the use of corticotherapy [85].

Conversely, autoantibodies can also contribute to control the pathogenic process resulting from an excess of inflammation. The specific autoimmune response to some cytokines or mediators has been proposed as a way to regulate their generation excess as it was demonstrated for autoantibodies to Interleukin (IL-6), but also to other cytokines [29–31, 86]. This could be the case for autoantibodies to Interleukin 8 (IL-8), which remain irrelevant or asymptomatic as long as their concentration stays low, and their binding onto blood cells is not enhanced. We found that some patients with heparin Induced thrombocytopenia (HIT), and without anti Heparin-PF4 antibodies were reactive to IL-8 or its complexes with heparin. In that case, thrombocytopenia occurred rapidly following heparin therapy, which enhance bridging of IL-8 to blood cells. As IL-8 can bind heparin, itself reacting particularly with platelets and endothelial cells, especially activated platelets, this triggers anti-IL-8 autoantibodies onto these cells, where an anti-IL-8 immune response focuses. This phenomenon then generates a HIT-like syndrome, producing thrombocytopenia and sometimes disseminated thrombosis [87,88]. A similar complication can develop in the presence of preexisting anti-PF4 autoantibodies if patients receive heparin [89,90]. A rapid HIT onset can develop and it reverses with heparin withdrawal [89]. In VITT, autoantibodies to some PF4 epitopes, especially those defining the PF4 heparin binding domain, are generated and provoke a severe thrombocytopenia, with thrombosis occurring at unusual cites, like the splanchnic vein, although heparin is absent [65, 66, 72]. This complication is often life-threatening, and anti-PF4 autoantibodies' concentration is roughly associated with disease severity and evolution. The association of autoantibody concentration and avidity with severity of autoimmune burden is a confirmed key feature and constitutes a major risk factor for their pathogenicity of clinically relevance.

6. Autoantibodies detected in patients with Covid-19

In Covid-19, as in many infectious diseases, autoimmune complications have been suspected early, and especially associated with long-lasting syndromes [91–93]. There is now evidence that the SARS-Cov-2 infection like cytomegalovirus, is among the infectious diseases, which are capable of triggering many different autoantibodies like Epstein Barr virus, or HIV infections. As in many infectious states, the emerging part of the "autoimmune iceberg" is detected through the identification of LA activity, IgG or IgM anti-cardiolipin/anti-phospholipid antibodies, or thrombocytopenia [39, 94, 95]. These observations are mainly the "side effect" of autoantibodies, which are targeted to phospholipid binding proteins, directly, like β2-Glyco-Protein 1, or indirectly, through divalent cations, like prothrombin, Protein S, Protein C or Annexin 5. Many other autoantibodies, forming complexes with self-proteins, are able to bind to phospholipid surfaces present on all cells, which are exposed with a high density of anionic phospholipids when activated, like platelets. This interaction competes with the targeted initiation of coagulation pathways and generates an apparent anticoagulant response (through steric hindrance for the binding of functional phospholipid binding proteins), although those autoantibodies are associated with thrombotic complications. In addition, the exacerbated inflammatory response in many Covid-19 patients generates NETosis, containing electronegative DNA complexed with histones and other blood proteins or immune complexes, contributing to increase the thrombotic risk [96–98]. NETosis can contribute to stimulate an autoimmune response, which worsens the disease evolution. The presence of anti-PF4 autoantibodies, not associated with HIT, has been reported recently in very severe clinical Covid-19 cases [99]. More generally, as heparin is frequently used to treat the thrombotic complications in Covid-19 patients, HIT can develop and requires the replacement of heparin by another anticoagulant [100,101].

Development of autoimmune complications in Covid-19 is suspected: i) from the characteristic clinical presentation in some patients; ii) from the presence of long-lasting effects with a persistent hyper-inflammatory state, and iii) from laboratory testing for some associated activities, like that of LA or thrombocytopenia [39,94]. A more accurate analysis needs to focus on which mechanisms can induce the development of these autoantibodies, which are reported to be very heterogenous, and how the autoantigen responsible for that autoimmune response is generated. Pathogens need an entry door to infect their targeted cells. That is provided usually by a cell surface receptor which interacts with a pathogen structure. That mechanism is of special relevance for viruses, which need the infected cell machinery to reproduce themselves and to expand through the body. Binding of viruses to specific cell surface receptors can then interfere in physiological functions, depending on the biological role of the concerned receptors. If these cell surface binding proteins are highly specific for a cell line or an organ, infection will be limited to these targets. However, if receptors are more ubiquitous, and are present on many cell lines or organs, the infection is then more extended and concerns different sites. This is the case for SARS-Cov-2, whose entry door is the Angiotensin Converting Enzyme 2 (ACE2) receptor, present at a high density on epithelial lung and pharyngeal cells, but also on many other cell lines and organs, like endothelial cells, kidneys, liver, heart, brain, spleen, pancreas, and nerves. Disease evolution depends then on the "race" between virus reproduction, its expansion and diffusion throughout the body, the development of the first innate immune response, with inflammation, neutrophils and macrophages activation, production of cytokines, and later, the adaptive immune cellular and humoral responses. This fight is complicated by other contributors, resulting from the side effects generated, like the cytokine storm, with thrombo-inflammation, highly stimulated by NETs. Although beneficial to slow down the progress of viral infection, NETs can become harmful and highly thrombogenic when present at too a high concentration, and are generate high kinetics [97,98]. Yet, another player can join the battle when autoantibodies are induced. The adaptive immune response goal is to generate specific antibodies to bind and remove viruses. These antibodies are targeted to viral proteins. However, some viral proteins have mimicry with human structures, and therefore cross-react with them, behaving like autoantibodies. In addition, the viral proteins or peptides targeted by the immune defense against the viral infection can be in intimate complexes with body's structures, usually proteins. In a first step, the immune response is specific to viral structures. But sometimes this response can be misdirected and antibodies are targeted to the whole complex, also becoming reactive with the body's self-protein. Autoantibodies are then generated.

7. Autoantibody characteristics in covid-19 patients

We early speculated that specific and high affinity reaction of the SARS-Cov-2 viral spike protein with ACE2 is a key situation for generating autoantibodies to ACE2 [8]. This idea was shared by others, and some speculative papers proposed the potential development of these autoantibodies in Covid-19 patients [9–11]. In a subsequent study on hospitalized Covid-19 patients, with various grades of severity,including fatal cases, we identified the presence of autoantibodies to ACE2, of IgG, IgM or IgA isotypes, or a combination of them, in about 10% of patients, and many of these autoantibodies were detected at a very high concentration [102]. Other studies confirmed the development of these autoantibodies in Covid-19 patients [103,104]. At present, there is not yet evidence on the contribution of these autoantibodies to disease complications or worsening, but investigations are ongoing. The relevance of anti-ACE2 autoantibodies could be of importance according to

Table 2
Autoantibodies reported in Covid-19 patients and possible clinical consequences; ACE2: angiotensin converting enzyme 2; PF4: platelet factor 4; RAAS: renin angiotensin aldosterone system;.

Possible autoantibodies in Covid-19	Potential pathological effect
Anti-ACE2	Interference in RAAS? Kawasaki-like disease?
Anti nuclear antibodies	Unknown
Anti-interferon antibodies	Disease severity
Anti-endothelial antibodies	Vasculatis,
Lupus Anticoagulant / anti-phospholipid antibodies	Thrombocytopenia, thrombosis
Anti-ganglioside antibodies	Guillain Barre syndrome
Anti-Annexin A1	Impact regulation of inflammation?
Anti-PF4 (Covid-19 course)	Disease severity, thrombocytopenia, thrombosis
Anti-Heparin-PF4 (heparin treated patients)	Thrombocytopenia, Thrombosis, Severity of disease evolution

the key regulatory role of ACE2 for controlling hypertension, sodium cell balance, and diuresis among other functions to regulate the Renin-Angiotensin-Aldosterone System (RAAS) [105]. As neutrophils play a key role for innate immunity, NETosis and thrombo-inflammation, we also looked for the presence of autoantibodies to Annexin A1, which is a major neutrophil released protein with anti-inflammatory activity [106–108]. Surprisingly, autoantibodies to Annexin A1 were detected at a high to very high concentration, with mainly IgG isotypes, but sometimes IgM, IgA or a combination, in a significant group of patients (about 20%), with some association with disease severity. In addition, we had the opportunity to test a Hemophilia A patient suffering from long-lasting Covid-19 symptoms for more than 1 year (plasma kindly provided by Dr D Desprez, from the University-Hospital of Strasbourg, France), and we found a high concentration of autoantibodies to Annexin A1, which remained at a very high concentration throughout the follow-up, although at this stage there is no evidence on the association of those autoantibodies with the persistence of symptoms.

Other studies have reported different targets for autoantibodies present in Covid-19 patients. In particular, preexisting or newly generated autoantibodies to interferons have been reported and they could be associated to disease severity and prognosis [109,110]. These autoantibodies could be generated as a regulatory mechanism for controlling the excess of interferon release, but as for cytokines, in the presence of some extreme pathological conditions, they can deviate the immune response by interfering in their function. Among the autoantibodies described in patients with Covid-19 are those provoking Guillain--Barré syndrome, thrombocytopenia, and anti-nuclear antibodies [94, 111, 112]. Of special relevance is the Kawasaki disease, observed in a few children infected with SARS-Cov-2, which is an autoimmune vasculitis probably induced by autoantibodies to endothelial cells [113, 114]. Autoantibodies to ACE2, a receptor also present on endothelial cells, were already reported in 2010, in patients with Connective Tissue Disease [115].

8. Laboratory assays for diagnosis of autoantibodies

Laboratory methods are essential for characterizing autoimmune complications associated with or induced by Covid-19, and following their evolution. Testing helps to identify the autoantibody target, and when possible the autoantigen, and to estimate the antibody concentration and avidity, two key parameters associated with autoantibodies' pathogenicity. The techniques used are either global, or they involve a specific antigen for capturing autoantibodies and isotyping them. Global methods characterize autoantibodies to the targeted cell or organ autoantibodies, or evaluate their interference of some biological functions, like anticoagulant activity. For example, antibodies to endothelial cells, to platelets, to neutrophils, to phospholipids have been reported. When the accurate target autoantigen is identified, more specific assays are designed by using the purified protein for capturing the autoantibodies, isotyping and quantitating them. That specific approach was used for identifying autoantibodies to ACE2, to Annexin A1 or to interferons [102, 106, 108]. The laboratory methods developed for measuring autoantibodies involved in Covid-19 will be described later, in a separate report.

9. Persistence of autoantibodies

Transitory autoantibodies reach a concentration peak, before progressively declining. When present, their biological effects persist for some time, and are detectable for several weeks or a few months, but their immunological detection can last for a longer time, up to 6 months or more. If autoantibodies become chronic, they can then stay at a high concentration, and remain active. What induces the switch to long-lasting autoantibodies and the evolution to a chronic autoimmune disease remains poorly understood. Genetic factors and individual predispositions could be involved, and some immunological system dysfunctions could lead to a misdirected response. With the availability of accurate tools, the increasing identification of the specific autoantibody targeted epitopes on autoantigens, and the understanding of circumstances favoring the development of autoimmune complications; a

better knowledge of this field is being generated.(Table 2).

10. Discussion and conclusions

The Covid-19 disease produced by the SARS-Cov-2 viral infection is characterized by the strong innate and adaptive responses associated with an exacerbated inflammatory reaction, and a cytokine storm [1,2]. This excess of immunological activity contributes to disease severity, morbidity and mortality. Neutrophils activity and NETosis play an important role, and, if they participate in the body's defense against viral infection and expansion, they also contribute to develop the thrombo-inflammatory syndrome, with a high incidence of thrombo-embolic complications [97,98]. Patients might develop enormous hemostatic abnormalities and biomarkers of hypercoagulability with a high thrombotic tendency. In affected patients, there is an increase of von Willebrand Factor (vWF), fibrinogen and Factor VIII, a tendency to antithrombin decrease, a high increase of plasminogen activator inhibitor 1 activity and protein concentration, and a low fibrinolysis potential. DDimer is very elevated, and is used as an essential indicator of disease severity. Severe cases have benefitted from anticoagulant therapies using heparin, especially unfractionated, and anti-inflammatory treatments, like dexamethasone [116]. This has contributed to significantly decrease the disease associated mortality rate.

Autoimmune complications can be an additional contributor to disease burden. They are involved in the disease course of various pathogen infections, especially with Cytomegalovirus, Epstein Barr or Human Immunodeficiency Virus. For the SARS-Cov-2 infection, involvement of autoimmune processes appears to be relevant, with a high variety of autoantibody targets, many being pan-specific, and anti-endothelial observed in various diseases, like anti-phospholipids, antibodies, or thrombocytopenia. Others could be more specific and linked to the viral strategy to infect human cells, through its specific binding to ACE2 [102–104]. The mechanisms underlying the induction of these various autoantibodies in certain patients could involve the many possibilities including antigen mimicry, and epitope spreading, like in most acquired autoimmune complications, as recently reviewed for VITT [117].

Apart from the identification of some autoimmune reactivities in patients suffering from Covid-19, and their possible association with disease severity and evolution, clinical studies on large cohorts are still missing. One could expect that availability of laboratory tools can contribute to perform transversal and longitudinal clinical studies to understand and document the contribution of autoantibodies to the disease prognosis.

The ongoing new omicron subvariants in combination with two other respiratory infections having similar symptoms, namely influenza (flu), and respiratory syncytial virus (RSV), all appearing with the coming colder season [as a Triple- endemic] are among some of the unmet high priority issues to be resolved. Needless to highlight that we must keep our immunity as high as possible and avoid reinfections as well as reduce the risk of long COVID that can occur these in cold days ahead even in the young.

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