SARS-CoV-2 and Autoimmune Cytopenia

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is associated with a variety of clinical manifestations related to viral tissue damage, as well as a virally induced immune response. Hyperstimulation of the immune system can serve as a trigger for autoimmunity. Several immune-mediated manifestations have been described in the course of SARS-CoV-2 infection. This review highlights COVID associated autoimmune hemolytic anemia and immune thrombocytopenic purpuria (ITP).

Keywords: autoimmune ; cytopenia ; autoimmune hemolytic anemia ; cold agglutinin syndrome ; COVID-19 ; SARS-CoV-2 ; ITP ; immune thrombocytopenia

1. Introduction

Since the first case of infection with novel SARS-CoV-2 virus was reported in Wuhan China in December of 2019, over 166 million people have been diagnosed and 3.4 million have died worldwide, as of 22 May 2021, and 1.6 billion doses of SARS -CoV-2 vaccines have been distributed [1]. This pandemic has had a devastating impact on human lives and has brought immense burden to the healthcare system. Symptoms of the infection range from asymptomatic infection, in at least 30% of cases [2], and mild respiratory illness, to severe complications, such as acute respiratory distress syndrome (ARDS) and multi-organ failure [3].

Activation of the immune system induced by SARS -CoV-2 can also contribute to the disease pathogenesis and organ damage. Immune hyperstimulation and dysregulation can lead to marked cytokine release syndrome, macrophage activation, and systemic hyperinflammation. Supporting the role of the inflammation-induced tissue damage, immunomodulatory and immunosuppressive agents have shown to have efficacy in the treatment of coronavirus disease 2019 (COVID-19), particularly in severe cases [4].

Hyperactivation of the immune system can trigger autoimmune manifestations in patients with prior history of autoimmune disease, as well as prompt the development of de novo autoimmune manifestations. Infections are an established risk factor for the development of autoimmune cytopenias. Viral infections linked to autoimmune hematologic disorders include the human immunodeficiency virus, hepatitis C virus and cytomegalovirus, parvovirus B19, Epstein–Barr virus, and Zika virus [5][6][7]. SARS-CoV-2 infection has been associated with several autoimmune complications, including cutaneous rashes and vasculitis, autoimmune cytopenia, anti-phospholipid syndrome, central and peripheral neuropathy, myositis, and myocarditis [8][9]. In a systematic review of 94 patients with COVID-19 who developed hematologic autoimmune disorders in their course of infection, the most common hematologic autoimmune disorder was immune thrombocytopenic purpura (ITP), seen in 58%, followed by autoimmune hemolytic anemia (AIHA) in 23% [10].

2. COVID-19 and Activation of the Immune System

Cytokine storm syndromes, such as ARDS and hemophagocytic lymphohistiocytosis (HLH), are seen in a subgroup of severely ill patients with COVID-19, supporting the role of the immune system dysregulation in the SARS-CoV-2 infection [11]. Both mild and severe forms of COVID-19 disease have been associated with changes in circulating leukocyte subsets and the upregulation of cytokine secretion, where marked increases in the secretion of cytokines of IL-6, IL-1β, IL-10, IL-17, TNF, and GM-CSF, referred to as ‘cytokine storm’, are seen in severe cases [12]. In addition, an imbalance in the Th17/Treg ratio and lower levels of regulatory T cells, which are involved in the downregulation of the immune response, have also been described in severe cases [13][14]. Mobilization of Th17 responses has been implicated in the pathogenesis of autoimmune diseases, including autoimmune hemolytic anemia [15][16], and low levels of regulatory CD4 T cells have been seen in patients with warm AIHA and ITP [17][18]. Lower levels of regulatory T cells in COVID-19 patients with severe infections can explain the higher rate of ITP in severe cases [19].

Multiple autoantibodies have been reported in association with SARS-CoV-2 infection, including antinuclear antibodies, cytoplasmic anti-neutrophil cytoplasmic antibodies, perinuclear anti-neutrophil cytoplasmic antibodies, anti-actin antibodies, and anti-mitochondrial antibodies [9]. High rates of lupus anticoagulant positivity rates associated with thrombosis, as well as anticardiolipin (aCL) and beta2 glycoprotein I (β2GPI), were reported in patients with COVID-19 infection [20][21]. Anti-heparin/platelet factor 4 (PF4) antibodies, which are associated with platelet activation in heparin-induced thrombocytopenia (HIT), have been recognized in severely ill COVID-19 patients with a HIT syndrome [22]. Some cases of HIT and positive PF4 antibodies have been reported without prior heparin exposure [23]. Antibodies to ADAMTS-13, a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13, with a clinical syndrome of thrombotic thrombocytopenic purpura (TTP), were described as well [24][25].

Cross-reactivity between SARS-CoV-2 proteins and a variety of tissue antigens has been reported [26][27], supporting the role of molecular mimicry in the development of autoantibodies [28]. A structural similarity between ankyrin 1, a red blood cell membrane adaptor protein defective in patients with hereditary spherocytosis, and the SARS-CoV-2 surface glycoprotein, named the “spike protein”, has been demonstrated [29]. A positive direct antiglobulin (DAT) test, which detects the presence of antibodies and or complement on the surface of red blood cells, has been reported in 13% of 267 anemic COVID-19 patients in one study, with higher rates of positivity in the ICU patients [30]. Another study reported a positive DAT in 46% of the 113 patients with COVID-19 [31].

In addition, greater than one-third of the immunogenic proteins in SARS-CoV-2 have been shown to have homology to proteins essential in the human adaptive immune system, providing support to the role of pathogenic priming in disease severity by induction of autoimmunity [32]. Induction of the autoimmune response against proteins in the adaptive immune system can impair major histocompatibility complex (MHC) class I and class II antigen presentation, cross-presentation of exogenous antigens, and programmed cell death protein 1 (PD-1) signaling [32], further contributing to immune dysregulation.

3. SARS-CoV-2 Infection in Patients with History of Autoimmune Disease

Patients with a history of autoimmune disease are potentially at risk for SARS-CoV-2 infection due to underlying immune dysregulation and use of immunosuppressive therapies. Alternatively, many immunomodulatory agents used in autoimmune diseases are utilized in the therapy of severe SARS-CoV-2 infection and can potentially curb the immune response and associated organ damage. It appears that SARS-CoV-2 infection in patients with autoimmune diseases runs a generally mild course, comparable to that of the general population. A cross-sectional study of 916 patients with autoimmune rheumatologic disorders in Italy identified 148 symptomatic patients. Symptoms were typically mild and similar to the general population and no deaths were seen [33]. A case registry of 600 patients from 40 countries from the Global Rheumatology Alliance reported a more severe course, with 46% patients requiring hospitalization and 9% resulting in death [34]. In a prospective case series of 86 patients with a history of immune-mediated inflammatory diseases treated with anticytokine biologics and/or other immunomodulatory therapies who developed confirmed or highly suspected symptomatic SARS-CoV-2 infection, the incidence of hospitalization was 16%, with one case of mortality among 14 admitted patients. This was comparable to the incidence of hospitalization in the general population [35].

With regards to SARS-CoV-2 infection in autoimmune cytopenias, in a cohort of 501 patients in northern Italy with autoimmune cytopenias, which included 139 patients with warm AIHA (wAIHA), 108 patients with cold agglutinin disease (CAD), and 103 patients with ITP, four patients developed SARS-CoV-2 pneumonia. Among those, three patients had autoimmune hemolytic anemia (one CAD, one wAIHA, and one Evan’s syndrome) and one had ITP. Relapse of hemolysis was seen in one patient with CAD and one with Evan’s syndrome, and was successfully treated with transfusion and steroids [36]. An unfortunate case of recurrent warm autoimmune hemolytic anemia in the setting of COVID-19 infection complicated by lethal cryptococcal sepsis and encephalitis in the setting of immunosuppression with cyclophosphamide and steroids has been reported as well [37].

In the largest series of 32 chronic ITP patients who tested positive for SARS-CoV-2 a median of 39 months after ITP diagnosis, 56% of patients had moderate to severe COVID-19 disease requiring hospitalization and 38% of patients required non-invasive or invasive ventilation [38]. However, the authors note that cases of mild or asymptomatic SARS-CoV-2 infection may have been missed given that many patients during this time were followed via telemedicine and patients were only tested if they sought medical care for COVID-19 symptoms. A total of 47% of patients had a relapse of ITP requiring treatment an average of 9 days after SARS-CoV-2 diagnosis. The patients who required hospitalization had higher rates of ITP relapse than the patients who did not require hospitalization (74% vs. 15%, $p = 0.006$), suggesting that relapse is more common in patients with more severe COVID-19 symptoms. Most patients who required treatment received corticosteroids, and the two patients who did not respond to corticosteroids and intravenous immunoglobulin (IVIG) expired from respiratory failure from COVID-19 disease. Given that almost half of the patients who had SARS-CoV-

2 experienced a relapse of ITP, clinicians should carefully monitor patients with a history of ITP who test positive for SARS-CoV-2 for bleeding symptoms. The mortality rate in this study was 9%, and death was related to SARS-CoV-2 severity rather than bleeding associated with ITP.

Interestingly, another smaller case series of eight patients with chronic ITP who had SARS-CoV-2 showed that four (50%) of the patients presented with early thrombocytosis and three patients required antiplatelet therapy, ITP treatment discontinuation, or ITP treatment reduction [39]. The authors speculate that lymphopenia could be responsible for the thrombocytosis, given that ITP is caused by auto-reactive B cells and altered regulatory T lymphocytes. Two patients (25%) had relapsed ITP and these patients showed a rapid response to treatment. Larger case series of patients with chronic ITP and subsequent SARS-CoV-2 infection are needed in order to clarify the association of thrombocytosis with SARS-CoV-2 infection.

4. SARS-CoV-2 as a Trigger for Development of Autoimmune Cytopenia

Table 1 summarizes reports of 15 patients who developed with cold agglutinin syndrome (CAS) in the setting of SARS-CoV-2 infection. The majority (nine) were males, and in five patients CAS was present at diagnosis. Hemolysis developed 5–20 days after the presentation in the rest of the patients. Four patients deceased as a consequence of SARS-CoV-2 infection and complications. In all other cases with available information, hemolysis resolved and patients recovered. Rituximab therapy [40] and plasma exchange were successfully used in one case each [41].

Table 1. CAS associated with SARS-CoV-2 infection.

Age/ Gender	Comorbidity	Symptoms to AIHA Development, Days	AIHA Treatment	AIHA Outcome	COVID Outcome	Author
62 Male	HTN, oropharyngeal squamous cell carcinoma on chemoradiation	16	Transfusion	Resolved	recovered	Capes [53]
24 Female	None	4	None	Resolved	recovered	Moonla [54]
51 Female	breast DCIS post-mastectomy on chemoradiation	0	Transfusion Steroids	Resolved	Recovered	Patil [55]
48 Male	HTN, DM1, obesity ESRD on peritoneal dialysis	7	None	Unknown	Deceased concurrent DVT, stroke	Maslov [56]
46 Female	ITP, asthma, splenectomy	0	Transfusion	Unknown	Deceased	Zagorski [57]
80 Female	Stage A CLL	12	None	Resolved	recovered	Nesr [58]
45 Male	Unknown	0	Transfusion	Unknown	Unknown	Raghuwanshi [59]
77 Male	COPD, G6PD deficiency	0	Steroids	Unknown	Deceased	Gupta [60]
61 Male	DM2, hypercholesterolemia, ESRD, CAD, atrial fibrillation	5	Steroids	Minimal hemolysis; Resolved	Recovered	Kaur [61]
70 Male 67 Male	Unknown Unknown	5 10	None None	Minimal Hemolysis Minimal Hemolysis	Unknown Deceased	Jensen [62]
43 Female 63 Male	untreated MS HTN	16 20	Transfusion Unknown	Recovered Recovered	Recovered Recovered	Huscenot [63]
69 Female	Stage IV CLL on tirabrutinib, discontiniued	18	Steroids, Rituximab IVIG	Resolved	Recovered concurrent ITP, myositis	Aldaghlawi [52]

Age/ Gender	Comorbidity	Symptoms to AIHA Development, Days	AIHA Treatment	AIHA Outcome	COVID Outcome	Author
54 Male	None	0	Steroids, Plasma exchange	Resolved	Recovered	Ramos-Ruperto [51]

CAD—coronary artery disease, CLL—chronic lymphocytic leukemia, COPD—chronic obstructive pulmonary disease, DCIS—ductal carcinoma in situ, DM—diabetes mellitis, ESRD—end stage renal disease, G6PD—glucose-6-phosphate dehydrogenase, ITP—immune thrombocytopenic purpura, HTN—hypertension, IVIG—intravenous immunoglobulin, MS-multiple sclerosis, PE-pulmonary embolism, DVT-deep vein thrombosis.

Immune thrombocytopenic purpura (ITP) has been described in numerous case reports and case series in association with SARS-CoV-2. The incidence of ITP in SARS-CoV-2 has been described in one study as 0.34% [42].

The majority of new cases of ITP in SARS-CoV-2 patients have been reported in patients 50–70 years old [10][19][42][43][44][45][46], although cases in children as young as 1 year and up to age 95 have been reported [42][47]. There have been two reported cases of pregnant women who developed de novo ITP associated with SARS -CoV-2 [42][48]. The increase in prevalence in older age is similar to ITP not associated with SARS -CoV-2 [49][50]. Unlike traditional ITP, SARS-CoV-2-associated ITP does not appear to be more common in younger females than in younger males, although the limited number of cases reported in patients younger than 50 might mask this association [10].

However, ITP can occur in patients with mild symptoms, and in one study, 7% of ITP cases were in patients with asymptomatic COVID-19 [19]. This underscores the importance of ruling out SARS-CoV-2 in new ITP cases even if there are no COVID-19 symptoms. As the pandemic continues, patients with newly diagnosed ITP should be tested for SARS -CoV-2 in addition to other classic viral triggers.

5. Current Insights

Viral infections have been established as a risk factor for the development of autoimmune cytopenia. In SARS-CoV-2 infection, the inflammatory response leads to hyperstimulation of the immune system, which can promote the development of autoimmune complications in the susceptible individuals. Recognizing autoimmune cytopenia in COVID-19 is important in order to avoid a delay in treatment. Patients with a more severe clinical course are more likely to have lower hemoglobin and platelet levels, and there is a strong association between anemia and thrombocytopenia with poor outcome/mortality in hospitalized patients with SARS-CoV-2 [30][51].

Homology between the ankyrin-1 and the SARS-CoV-2 spike glycoprotein can lead to the development of red cell autoantibodies and potentially autoimmune hemolytic anemia in response to viral infection or vaccination. This can account for high rates of DAT positivity in patients with SARS-CoV-2 infection. It is important to note that a positive direct anti-globulin test can be seen in the absence of changes in the hemolytic parameters in healthy adults as well as hospitalized patients [15], and, in those cases, is not associated with clinical syndrome of autoimmune hemolytic anemia. A similar homology between SARS-CoV-2 and platelet antigens has not yet been reported.

Most cases of wAIHA that developed in the setting of SARS-CoV-2 infection were generally self-limited and responded to steroids and supportive measures. Rituximab administration was utilized in less than half of the patients. One mortality seen in a case of recurrent warm autoimmune hemolytic anemia triggered by SARS-CoV-2 infection was due to opportunistic infection in the setting of immunosuppression with cyclophosphamide and steroids. Generally favorable outcomes in patients with wAIHA suggest the importance of limiting the use of cytotoxic agents in treating autoimmune cytopenias in SARS-CoV-2 in favor of steroids and rituximab in refractory cases.

Cold agglutinin syndrome was seen in approximately 50% of the cases of AIHA in association with SARS-CoV-2 reported in the literature, compared to the reported overall 20–25% incidence in idiopathic AIHA [52]. In contrast, most cases of infection-related AIHAs are usually cold, IgM-mediated, and self-limited. Four out of fifteen patients with cold agglutinin syndrome in the setting of COVID 19 deceased as a result of SARS-CoV-2 infection, suggesting a higher mortality rate in this population. Complement activation plays a key role in the pathophysiology of cold autoimmune hemolytic anemia. The crucial and detrimental role of complement activation and preliminary efficacy of complement inhibition has been previously described in SARS-CoV-2 infection [53]. The presence of cold agglutinin syndrome can serve as a potential marker of adverse outcomes in SARS-CoV-2 infection and of consideration for immunomodulatory and/or complement directed therapy. Complement involvement was seen in almost two thirds of the reported cases of wAIHA in the setting of SARS-CoV-2 infection, which is much higher compared to primary wAIHA cases, with a large retrospective study reporting

30% of cases positive for IgG and complement [54]. However, clinical outcomes were much more favorable in wAIHA. Therapy was required more frequently in COVID-19-associated wAIHA compared to COVID-19-associated CAS, which is consistent with the need for therapy in idiopathic forms [17].

ITP associated with SARS-CoV-2 is more common in older adults and is infrequently seen in children. Thrombocytopenia typically occurs after 1 week of symptoms. Most patients with ITP are seen in patients with moderate to severe infection requiring oxygen. However, a significant portion can develop ITP with asymptomatic SARS-CoV-2 infection, suggesting that as the pandemic continues, the evaluation for SARS-CoV-2 should be included in the initial evaluation for viral etiologies for new onset immune thrombocytopenia. Bleeding might be more common than in ITP not associated with SARS-CoV-2; however, this could be due to anticoagulation used for coagulopathy, and larger studies need to be carried out. Similar to wAIHA, most cases of ITP associated with SARS-CoV-2 respond well to first line therapies such as steroids and IVIG.

References

1. COVID-19 Map. Johns Hopkins Coronavirus Resource Center. Available online: https://coronavirus.jhu.edu/map.html (accessed on 31 May 2021).
2. Nishiura, H.; Kobayashi, T.; Miyama, T.; Suzuki, A.; Jung, S.-M.; Hayashi, K.; Kinoshita, R.; Yang, Y.; Yuan, B.; Akhmetzhanov, A.R.; et al. Estimation of the asymptomatic ratio of novel coronavirus infections (COVID-19). Int. J. Infect. Dis. 2020, 94, 154–155.
3. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. Lancet 2020, 395, 497–506.
4. Esmaeilzadeh, A.; Elahi, R. Immunobiology and immunotherapy of COVID-19: A clinically updated overview. J. Cell. Physiol. 2021, 236, 2519–2543.
5. Smatti, M.K.; Cyprian, F.S.; Nasrallah, G.K.; Al Thani, A.A.; Almishal, R.O.; Yassine, H.M. Viruses and Autoimmunity: A Review on the Potential Interaction and Molecular Mechanisms. Viruses 2019, 11, 762.
6. Cines, D.B.; Liebman, H.; Stasi, R. Pathobiology of Secondary Immune Thrombocytopenia. Semin. Hematol. 2009, 46, S2–S14.
7. Smalisz-Skrzypczyk, K.; Romiszewski, M.; Matysiak, M.; Demkow, U.; Pawelec, K. The Influence of Primary Cytomegalovirus or Epstein-Barr Virus Infection on the Course of Idiopathic Thrombocytopenic Purpura. In Advances in Clinical Science; Springer: Cham, Switzerland, 2015; pp. 83–88.
8. Talotta, R.; Robertson, E. Autoimmunity as the comet tail of COVID-19 pandemic. World J. Clin. Cases 2020, 8, 3621–3644.
9. Tang, K.-T.; Hsu, B.-C.; Chen, D.-Y. Autoimmune and Rheumatic Manifestations Associated With COVID-19 in Adults: An Updated Systematic Review. Front. Immunol. 2021, 12, 645013.
10. Taherifard, E.; Taherifard, E.; Movahed, H.; Mousavi, M.R. Hematologic autoimmune disorders in the course of COVID-19: A systematic review of reported cases. Hematology 2021, 26, 225–239.
11. Mehta, P.; McAuley, D.; Brown, M.; Sanchez, E.; Tattersall, R.S.; Manson, J.J. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet 2020, 395, 1033–1034.
12. Wang, J.; Jiang, M.; Chen, X.; Montaner, L.J. Cytokine storm and leukocyte changes in mild versus severe SARS-CoV-2 infection: Review of 3939 COVID-19 patients in China and emerging pathogenesis and therapy concepts. J. Leukoc. Biol. 2020, 108, 17–41.
13. Qin, C.; Zhou, L.; Hu, Z.; Zhang, S.; Yang, S.; Tao, Y.; Xie, C.; Ma, K.; Shang, K.; Wang, W.; et al. Dysregulation of Immune Response in Patients with Coronavirus 2019 (COVID-19) in Wuhan, China. Clin. Infect. Dis. 2020, 71, 762–768.
14. Liu, Y.; Zhang, C.; Huang, F.; Yang, Y.; Wang, F.; Yuan, J.; Zhang, Z.; Qin, Y.; Li, X.; Zhao, D.; et al. Elevated plasma levels of selective cytokines in COVID-19 patients reflect viral load and lung injury. Natl. Sci. Rev. 2020, 7, 1003–1011.
15. Barcellini, W.; Clerici, G.; Montesano, R.; Taioli, E.; Morelati, F.; Rebulla, P.; Zanella, A. In vitro quantification of anti-red blood cell antibody production in idiopathic autoimmune haemolytic anaemia: Effect of mitogen and cytokine stimulation. Br. J. Haematol. 2000, 111, 452–460.
16. Noack, M.; Miossec, P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. Autoimmun. Rev. 2014, 13, 668–677.

17. Barcellini, W.; Zaninoni, A.; Giannotta, J.A.; Fattizzo, B. New Insights in Autoimmune Hemolytic Anemia: From Pathogenesis to Therapy Stage 1. J. Clin. Med. 2020, 9, 3859.

18. Li, C.; Li, J.; Ni, H. Crosstalk Between Platelets and Microbial Pathogens. Front. Immunol. 2020, 11, 1962.

19. Bhattacharjee, S.; Banerjee, M. Immune Thrombocytopenia Secondary to COVID-19: A Systematic Review. SN Compr. Clin. Med. 2020, 2, 2048–2058.

20. Gil, M.R.; Barouqa, M.; Szymanski, J.; Gonzalez-Lugo, J.D.; Rahman, S.; Billett, H.H. Assessment of Lupus Anticoagulant Positivity in Patients with Coronavirus Disease 2019 (COVID-19). JAMA Netw. Open 2020, 3, e2017539.

21. Pascolini, S.; Vannini, A.; Deleonardi, G.; Ciordinik, M.; Sensoli, A.; Carletti, I.; Veronesi, L.; Ricci, C.; Pronesti, A.; Mazzanti, L.; et al. COVID-19 and Immunological Dysregulation: Can Autoantibodies be Useful? Clin. Transl. Sci. 2021, 14, 502–508.

22. Patell, R.; Khan, A.M.; Bogue, T.; Merrill, M.; Koshy, A.; Bindal, P.; Joyce, R.; Aird, W.C.; Neuberg, D.; Bauer, K.A.; et al. Heparin induced thrombocytopenia antibodies in Covid-19. Am. J. Hematol. 2020, 95.

23. Riker, R.R.; May, T.L.; Fraser, G.L.; Gagnon, D.J.; Bandara, M.; Zemrak, W.R.; Seder, D.B. Heparin-induced thrombocytopenia with thrombosis in COVID-19 adult respiratory distress syndrome. Res. Pr. Thromb. Haemost. 2020, 4, 936–941.

24. Hindilerden, F.; Yonal-Hindilerden, I.; Akar, E.; Kart-Yasar, K. Covid-19 associated autoimmune thrombotic thrombocytopenic purpura: Report of a case. Thromb. Res. 2020, 195, 136–138.

25. Albiol, N.; Awol, R.; Martino, R. Autoimmune thrombotic thrombocytopenic purpura (TTP) associated with COVID-19. Ann. Hematol. 2020, 99, 1673–1674.

26. Vojdani, A.; Kharrazian, D. Potential antigenic cross-reactivity between SARS-CoV-2 and human tissue with a possible link to an increase in autoimmune diseases. Clin. Immunol. 2020, 217, 108480.

27. Kanduc, D.; Shoenfeld, Y. Molecular mimicry between SARS-CoV-2 spike glycoprotein and mammalian proteomes: Implications for the vaccine. Immunol. Res. 2020, 68, 310–313.

28. Liu, Y.; Sawalha, A.H.; Lu, Q. COVID-19 and autoimmune diseases. Curr. Opin. Rheumatol. 2021, 33, 155–162.

29. Angileri, F.; Légaré, S.; Gammazza, A.M.; De Macario, E.C.; Macario, A.J.L.; Cappello, F. Is molecular mimicry the culprit in the autoimmune haemolytic anaemia affecting patients with COVID-19? Br. J. Haematol. 2020, 190.

30. AlGassim, A.A.; Elghazaly, A.A.; Alnahdi, A.S.; Mohammed-Rahim, O.M.; Alanazi, A.G.; Aldhuwayhi, N.A.; Alanazi, M.M.; Almutairi, M.F.; Aldeailej, I.M.; Kamli, N.A.; et al. Prognostic significance of hemoglobin level and autoimmune hemolytic anemia in SARS-CoV-2 infection. Ann. Hematol. 2021, 100, 37–43.

31. Berzuini, A.; Bianco, C.; Paccapelo, C.; Bertolini, F.; Gregato, G.; Cattaneo, A.; Erba, E.; Bandera, A.; Gori, A.; Lamorte, G.; et al. Red cell–bound antibodies and transfusion requirements in hospitalized patients with COVID-19. Blood 2020, 136, 766–768.

32. Lyons-Weiler, J. Pathogenic priming likely contributes to serious and critical illness and mortality in COVID-19 via autoimmunity. J. Transl. Autoimmun. 2020, 3, 100051.

33. Zen, M.; Fuzzi, E.; Astorri, D.; Saccon, F.; Padoan, R.; Ienna, L.; Cozzi, G.; Depascale, R.; Zanatta, E.; Gasparotto, M.; et al. SARS-CoV-2 infection in patients with autoimmune rheumatic diseases in northeast Italy: A cross-sectional study on 916 patients. J. Autoimmun. 2020, 112, 102502.

34. Gianfrancesco, M.; Hyrich, K.L.; Al-Adely, S.; Carmona, L.; Danila, M.I.; Gossec, L.; Izadi, Z.; Jacobsohn, L.; Katz, P.; Lawson-Tovey, S.; et al. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: Data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann. Rheum. Dis. 2020, 79, 859–866.

35. Haberman, R.; Axelrad, J.; Chen, A.; Castillo, R.; Yan, D.; Izmirly, P.; Neimann, A.; Adhikari, S.; Hudesman, D.; Scher, J.U. Covid-19 in Immune-Mediated Inflammatory Diseases—Case Series from New York. N. Engl. J. Med. 2020, 383, 85–88.

36. Barcellini, W.; Giannotta, J.A.; Fattizzo, B. Are Patients with Autoimmune Cytopenias at Higher Risk of COVID-19 Pneumonia? The Experience of a Reference Center in Northern Italy and Review of the Literature. Front. Immunol. 2021, 11, 609198.

37. Woldie, I.L.; Brown, I.G.; Nwadiaro, N.F.; Patel, A.; Jarrar, M.; Quint, E.; Khokhotva, V.; Hugel, N.; Winger, M.; Briskin, A. Autoimmune Hemolytic Anemia in a 24-Year-Old Patient With COVID-19 Complicated by Secondary Cryptococcemia and Acute Necrotizing Encephalitis: A Case Report and Review of Literature. J. Med. Cases 2020, 11, 362–365.

38. Mingot-Castellano, M.E.; Alcalde-Mellado, P.; Pascual-Izquierdo, C.; Perez Rus, G.; Calo Perez, A.; Martinez, M.P.; López-Jaime, F.J.; Perez, L.A.; Gonzalez-Porras, J.R.; Fernández, F.L.; et al. Incidence, characteristics and clinical profile of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection in patients with pre-existing primary immune thrombocytopenia (ITP) in Spain. Br. J. Haematol. 2021.
39. de la Cruz-Benito, B.; Rivas-Pollmar, M.I.; Álvarez Román, M.T.; Trelles-Martínez, R.; Martín-Salces, M.; Lázaro-del Campo, P.; Ramírez-López, A.; García-Barcenilla, S.; Cebanu, T.; Acuña-Butta, P.; et al. Paradoxical effect of SARS-CoV-2 infection in patients with immune thrombocytopenia. Br. J. Haematol. 2021, 192, 973–977.
40. Aldaghlawi, F.; Shammah, A.; Kio, E. SARS-CoV-2 infection complicated with cold agglutinin disease and myositis. Clin. Case Rep. 2021, 9, 2196–2199.
41. Ramos-Ruperto, L.; García-Pérez, E.; Hernández-Maraver, D.; Kerguelén-Fuentes, A.; Viejo-Llorente, A.; Robles-Marhuenda, Á.; Busca-Arenzana, C. A 3-Case Series of Autoimmune Haemolytic Anaemia and COVID-19: Is Plasma Exchange an Alternative? SN Compr. Clin. Med. 2021, 3, 1420–1423.
42. Kewan, T.; Gunaratne, T.N.; Mushtaq, K.; Alayan, D.; Daw, H.; Haddad, A. Outcomes and management of immune thrombocytopenia secondary to COVID-19: Cleveland clinic experience. Transfusion 2021.
43. Bomhof, G.; Mutsaers, P.G.; Leebeek, F.; te Boekhorst, P.; Hofland, J.; Croles, F.N.; Jansen, G. COVID-19-associated immune thrombocytopenia. Br. J. Haematol. 2020, 190, e61–e64.
44. Zulfiqar, A.-A.; Lorenzo-Villalba, N.; Hassler, P.; Andrès, E. Immune Thrombocytopenic Purpura in a Patient with Covid-19. N. Engl. J. Med. 2020, 382, e43.
45. Lévesque, V.; Millaire, É.; Corsilli, D.; Rioux-Massé, B.; Carrier, F.-M. Severe immune thrombocytopenic purpura in critical COVID-19. Int. J. Hematol. 2020, 112, 746–750.
46. Mahévas, M.; Moulis, G.; Andres, E.; Riviere, E.; Garzaro, M.; Crickx, E.; Guillotin, V.; Malphettes, M.; Galicier, L.; Noel, N.; et al. Clinical characteristics, management and outcome of COVID-19-associated immune thrombocytopenia: A French multicentre series. Br. J. Haematol. 2020, 190, e224–e229.
47. Kok, E.Y.; Srivaths, L.; Grimes, A.B.; Vogel, T.P.; Tejtel, S.K.S.; Muscal, E. Immune thrombocytopenia following multisystem inflammatory syndrome in children (MIS-C)—A case series. Pediatr. Hematol. Oncol. 2021, 1–8.
48. Tang, M.; Nur, E.; Biemond, B. Immune thrombocytopenia due to COVID-19 during pregnancy. Am. J. Hematol. 2020, 95, 191.
49. Dr, T.; Beebe, L.A.; Neas, B.R.; Vesely, S.K.; Segal, J.B.; George, J.N. Prevalence of primary immune thrombocytopenia in Oklahoma. Am. J. Hematol. 2012, 87, 848–852.
50. Frederiksen, H.; Schmidt, K. The Incidence of Idiopathic Thrombocytopenic Purpura in Adults Increases with Age. Blood 1999, 94, 909–913.
51. Maquet, J.; Lafaurie, M.; Sommet, A.; Moulis, G.; Alvarez, M.; Amar, J.; Attal, M.; Balardy, L.; Balen, F.; Beyne-Rauzy, O.; et al. Thrombocytopenia is independently associated with poor outcome in patients hospitalized for COVID-19. Br. J. Haematol. 2020, 190.
52. Sokol, R.J.; Hewitt, S.; Stamps, B.K. Autoimmune haemolysis: An 18-year study of 865 cases referred to a regional transfusion centre. BMJ 1981, 282, 2023–2027.
53. Risitano, A.M.; Mastellos, D.C.; Huber-Lang, M.; Yancopoulou, D.; Garlanda, C.; Ciceri, F.; Lambris, J.D. Complement as a target in COVID-19? Nat. Rev. Immunol. 2020, 20, 343–344, Erratum in: Nat. Rev. Immunol. 2020, 20, 448.
54. Barcellini, W.; Zaninoni, A.; Fattizzo, B.; Giannotta, J.A.; Lunghi, M.; Ferrari, A.; Leporace, A.P.; Maschio, N.; Scaramucci, L.; Cantoni, S.; et al. Predictors of refractoriness to therapy and healthcare resource utilization in 378 patients with primary autoimmune hemolytic anemia from eight Italian reference centers. Am. J. Hematol. 2018, 93, E243–E246.