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Hematologic Autoimmune Manifestation Secondary to Coronavirus Disease 19 Infection – A Single-Center Experience

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Abstract

BACKGROUND: Since December 2019, multiple human cases of novel coronavirus infection were reported, representing with upper respiratory symptoms (influenza-like presentation). The virus was named the severe acute respiratory system coronavirus 2 (SARS-COV-2). Studies have reported cases of patients with coronavirus disease 19 (COVID-19) infection, including development of several autoimmune events that suggest that infection with SARS-CoV-2 may be associated with initiation of autoimmune hematological autoimmune disorders.

AIM: This study aims to review the hematological autoimmune phenomena after infection with SARS-CoV-2 to assist into the pathogenic mechanisms, clinical manifestations, and treatment of this group of patients.

MATERIALS AND METHODS: This is a retrospective study that includes 21 patients with autoimmune diseases such as secondary immune thrombocytopenia (ITP), autoimmune hemolytic anemia (AIHA), and thrombotic thrombocytopenic purpura (TTP) that have emerged after COVID-19 infection. The patients were diagnosed and treated at the University Clinic of Hematology-Skopje for a period of time from January 2020 to April 2021.

RESULTS: The most common hematologic autoimmune disorder was ITP in 13 cases (62%) followed by AIHA in 5 cases (24%) and TTP in 3 individuals (14%). The mean time of onset of the hematologic autoimmune presentations was 18.4 ± 10.3 days. The therapy of this condition in patients with COVID-19 infection requires an individualized approach to achieve a precise balance between the risk of severe bleeding and of thromboembolic events.

CONCLUSION: Causal relationship between COVID-19 infection and these autoimmune events still requires further studies. We should all have in mind the risk of development of hematologic autoimmune disorders in infected patients.

Introduction

In December 2019, multiple human cases of the novel coronavirus infection were reported in Wuhan, China, in patients complaining of upper respiratory symptoms (influenza-like presentation). The virus was named severe acute respiratory system coronavirus 2 (SARS-CoV-2). Due to the high virulence rate of the newly discovered virus, various measures were taken worldwide to maintain social distance to prevent viral transmission and spread of the disease. However, despite the complete lockdown and social distancing in many countries around the world, a pandemic was declared by the World Health Organization (WHO) on March 11, 2020.

While SARS-CoV-2 mainly targets respiratory tract, resulting in respiratory failure and acute respiratory distress syndrome as the leading cause of death in diseased patients, clinical manifestations in different organs are very common. Common symptoms of SARS-CoV-2 infection (coronavirus disease 19 [COVID-19]) are fever, dry cough, fatigue, sore throat, malaise, and myalgia. Symptoms such as headache, dizziness, diarrhea, nausea, and vomiting are less frequent. While the majority of patients have only mild symptoms without progression to pneumonia or mild pneumonia, 14% of patients present with severe pneumonia and 5% of patients develop a critical disease leading to acute respiratory distress syndrome (ARDS), cardiac injury, renal injury, or multiorgan failure. Autoimmune disorders including immune thrombocytopenia (ITP), Guillain–Barré, and antiphospholipid syndrome have been described in association with SARS-CoV-2 infection. Recently, an increasing number of studies have shown that SARS-CoV-2 infection can result in altered immune system functions [1] and the vascular component of the disease is becoming more and more evident.

These changes can range from an inadequate immune response and abnormal cytokine or chemokine production to immune system hyperactivity and a dramatic increase in inflammatory parameters. These intense immune responses can lead to an autoimmune reaction and cytokine storm [2]. In addition, studies

have reported cases of patients with COVID-19 who developed severe autoimmune events [3]. These facts suggest that SARS-CoV-2 infection may be associated with initiation of autoimmune disorders. Among these autoimmune manifestations, several hematological autoimmune disorders have also been reported and these have been shown to complicate the clinical course of the disease, determining the outcome in patients with COVID-19 [4], [5], [6], [7].

Patients and Methods

This was a retrospective study that included 21 patients with hematological autoimmune diseases: ITP, autoimmune hemolytic anemia (AIHA), and thrombocytopenic purpura (TTP) that had emerged after SARS-CoV-2 infection. The patients were diagnosed and treated at the University Clinic of Hematology-Skopje in the period between January 2020 and April 2021. The diagnosis of ITP, AIHA, and TTP was defined according to the national guidelines.

All the patients were diagnosed with SARS-CoV-2 infection with a reverse transcriptase-polymerase chain reaction by nasopharyngeal swab. After the clinical presentation of the autoimmune hematological disease, all the patients were evaluated for clinical and laboratory variables which included sex, age, physical examination with evaluation of lymph nodes (cervical, axillary, and inguinal), measurement of liver and spleen size, blood cell counts (white blood cells, hemoglobin levels, and platelet counts), reticulocyte counts, peripheral blood smear, biochemistry analyses, haptoglobin levels, ferritin levels, direct antiglobulin test, ADAMTS 13, anti-ADAMTS 13 antibodies.

Response and complete response (CR) were defined according to standardized international criteria, for ITP: Platelet count of >30 × 10^9/l with at least doubling of the baseline value and platelet count of >100 × 10^9/l, respectively; for AIHA: Hemoglobin levels >100 g/L in absence of laboratory signs of hemolysis (normal reticulocyte counts, normal lactate dehydrogenase [LDH], and haptoglobin levels) [14]; and CR for TTP: Platelet count of >150 × 10^9/l, reticulocytes <100 × 10^9/l, LDH< 300U/l, and haptoglobin> 40 mg% [15]. According to the European Union and national general data protection regulations, all patients were informed about the study and data collection by a written letter detailing their rights. The study was approved by the Ethics Committee of the University Clinic of Hematology in Skopje, Republic of Macedonia.

Statistical analysis

Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) 23.0 software program (SPSS Inc., Chicago, IL, USA). Normally distributed data were expressed as mean ± standard deviation (SD), while non-parametric data were expressed in median (interquartile range, IQR).

Results

A total of 21 patients with SARS-CoV-2 infection who developed hematologic autoimmune disorders during the course of infection were included in the analysis. Male and female patients constituted an almost equal proportion of the study cases, more precisely, nine patients were male and 12 patients were female. The study cases had a wide age range, from 18 years to 81 years with a median age of 56 and a mean age of 54 ± 17.4. The majority of the patients (16 cases – 76%) had comorbidities. The most common presentation of SARS-CoV-2 infection in these cases was fever, reported in 11 (52%) of them followed by coughing in 10 (47%) and severe bronchopneumonia in 7 patients (33%) (Table 1). The most common hematologic autoimmune disorder was ITP, seen in 13 cases (62%) followed by AIHA in 5 cases (24%) and thrombotic TTP in 3 individuals (14%) (Table 1). The mean time of onset of the hematologic autoimmune presentations in relation to SARS-COv-2 infection for all categories of hematologic autoimmune disorders was 18.4+/-10.3 days. Among all patients with ITP, 5 (38.4%) patients had no apparent signs of bleeding at the time of diagnosis.

Among these patients, 19 patients recovered and their hematological indices related to the autoimmune disorders improved. Among the deceased cases, one was with ITP and the other one with TTP. In both cases, intracerebral hemorrhage was suspected. The patient with TTP died due to intracerebral hemorrhage within the first 24 h, before the initiation of plasma exchange. The patient with ITP passed away due to his poor condition. It may be concluded that the remission rate was 95% (19 out of 20 patients) in cases in which autoimmune disorder-oriented treatment was administered.

Treatment

Among the patients with ITP, majority of patients, namely, nine patients, received monotherapy with corticosteroids (dexamethasone 1–1.5 mg/kg d.). One patient, refractory to steroid treatment, received intravenous immunoglobulins (IVIG) (1 g/kg/d – 2 days) and thrombopoietin receptor agonists (eltrombopag – 50 mg/d). One patient received additional therapy with cyclosporin (5 mg/kg/d) and rituximab (375 mg/m^2 IV once weekly × 4), and splenectomy was performed due to poor response to

Table 1: Characteristics, treatment, and outcome of the COVID-19-induced autoimmune ITP, AIHA, and TTP patients

Patient initials	Gender and age	Patient's medical history	Clinical presentation at COVID-19 infection	Hematologic autoimmune manifestation	Timing of the hematologic presentations	Treatment	Outcome
Patient 1 A.S.	Male 31 years old	Hepatitis B	Cough, fever, severe bronchopneumonia	ITP	7 days	Dexamethasone (without response), IVIG, thrombopoietin	Recovered (response to thrombopoietin)
Patient 2 A.G.	Male 38 years old	/	Severe bronchopneumonia	ITP	5 days	Dexamethasone	Recovered (response to dexamethasone)
Patient 3 S.V.	Female 29 years old	Hepatitis B Hashimoto thyroiditis	Asymptomatic COVID 19 infection, petechial hemorrhage and bruising	ITP	20 days	Dexamethasone, (without response), splenectomy, cyclosporine, rituximab	Recovered (response to cyclosporine and rituximab)
Patient 4 D.S.	Female 56 years old	Type 2 diabetes hypertension obesity cardiomyopathy	Fever, cough, headache, fatigue, petechial hemorrhage	ITP	10 days	Dexamethasone, cyclosporine	Recovered (response to cyclosporine)
Patient 5 P.B.	Male 71 years old	Chronic obstructive pulmonary disease, benign prostatic hyperplasia	Severe bronchopneumonia	ITP	20 days	Dexamethasone, cyclosporine	Recovered (response to dexamethasone and cyclosporine)
Patient 6 D.N.	Female 67 years old	Hypertension	Asymptomatic COVID19 infection, petechial hemorrhage and bruising	ITP	30 days	Dexamethasone	Recovered (response to dexamethasone)
Patient 7 O.S.	Male 37 years old	/	Bronchopneumonia, fever, fatigue, petechial hemorrhage	ITP	20 days	Dexamethasone	Recovered (response to dexamethasone)
Patient 8 D.N.	Female 71 years old	Breast cancer, bipolar disorder	Asymptomatic COVID-19 infection	ITP	30 days	Dexamethasone	Recovered (response to dexamethasone)
Patient 9 D.A.	Female 73 years old	Hypertension, Type 2 diabetes	Asymptomatic COVID-19, petechial hemorrhage, and bruising	ITP	30 days	Dexamethasone	Recovered (response to dexamethasone)
Patient 10 K.S.	Female 18 years old	/	Asymptomatic COVID-19 infection, petechial hemorrhage, and bruising	ITP	20 days	Dexamethasone	Recovered
Patient 11 Lj. S.	Female 62 years old	/	Asymptomatic COVID-19 infection, petechial hemorrhage, and bruising	ITP	20 days	Dexamethasone	Recovered
Patient 12 V.P.	Male 68 years old	/	Severe bronchopneumonia, fever bruising	ITP	10 days	Dexamethasone	Recovered
Patient 13 PM	Male 81 years old	Hypertension	Fever, headache, dizziness, neurological manifestations	ITP	10 days	Dexamethasone	The lethal outcome
Patient 14 M.A.	Male 38 years old	Hypertension	Fever, cough, headache, fatigue	AIHA	30 days	Dexamethasone	Recovered
Patient 15 M.B.	Male 52 years old	Hypertension, Type 2 diabetes, obesity	Severe bronchopneumonia, fever, cough, headache, fatigue	AIHA	30 days	Dexamethasone, cyclosporine	Recovered (response to cyclosporine)
Patient 16 E.R.	Female 78 years old	Painful polyneuropathy, radiculopathy, hypertension	Asymptomatic COVID-19 infection	AIHA	At the time of COVID-19 testing	Dexamethasone	Recovered
Patient 17 S.P.	Female 43 years old	Chronic obstructive pulmonary disease	Asymptomatic COVID-19, petechial hemorrhage, and bruising	AIHA	30 days	Dexamethasone	Recovered
Patient 18 Z.A.	Female 58 years old	Leg ulcer (ulcus cruris), leg fracture	Cough, headache, fatigue	AIHA	15 days	Dexamethasone, azathioprine (Imuran)	Recovered
Patient 19 M.I.	Female 53 years old	Hypertension	Asymptomatic COVID-19 infection	TTP	14 days	Dexamethasone, plasmapheresis, cyclosporine, rituximab	Recovered
Patient 20 R.N.	Male 57 years old	Multiple myeloma, autologous stem cell transplant	Severe bronchopneumonia, fever, headache, dizziness, neurological manifestations	TTP	5 days	Dexamethasone	The lethal outcome
Patient 21 B.T.	Female, 55 years old	Hypothyroidism	Asymptomatic COVID-19 infection	TTP	20 days	Dexamethasone (osteoporosis due to corticosteroids), plasmapheresis, cyclosporine, rituximab	Recovered

ITP: Immune thrombocytopenia, AIHA: Autoimmune hemolytic anemia, TTP: Thrombocytopenic purpura, IVIG: Intravenous immunoglobulins, COVID-19: Coronavirus disease 19.

previous therapy. Two patients received therapy with corticosteroids and cyclosporine (Table 1). Among the patients treated with corticosteroids, therapeutic response was not achieved in four patients. These patients received second-line treatment with IVIG and other immunosuppressive drugs. All AIHA patients were treated with steroids or a combination of steroids and immunosuppressive drugs (Table 1). Patients with TTP were treated with plasmapheresis, corticosteroids, and immunosuppressive therapy.

Discussion

Hematologic autoimmune sequels in the patients infected with SARS-CoV-2 infection, observed in this study were ITP, AIHA, and TTP (syndrome Moskowitz). Although the exact mechanism of these immune complications is unknown, there are evidences suggesting a causal link between coronavirus infection and their occurrence.

Several viral infections such as HIV, hepatitis C virus, and Epstein–Barr virus have been associated with hematologic autoimmune disorders so far. Therefore, SARS-CoV-2 infection may be attributed to trigger a cascade of events, involving both the innate and adaptive immunity mechanisms, resulting in autoimmunity [8]. The number of all SARS-CoV-2-infected individuals in Macedonia in the period covered in the study was approximately 131,424.

In about one-third of patients with SARS-CoV-2 infection, mild-to-severe degree of thrombocytopenia is found. In this study, classic causes of thrombocytopenia, such as consumption coagulopathy, toxic shock,

heparin-induced thrombocytopenia, and thrombotic TTP, were excluded and in all patients with autoimmune mechanisms following SARS-CoV-2 infection, a series of tests were performed to rule out the classic causes of thrombocytopenia. In all cases, the diagnosis of ITP was established in absence of any demonstrable primary disease.

The occurrence of viral induction of autoimmunity can be explained in several ways, including molecular mimicry, cryptic antigen expression, and epitope spreading. Molecular mimicry is stimulation of the immune system through certain microbial antigens that can lead to generation of cross-reactive antibodies to certain glycoproteins on platelet surface. These antiplatelet antibodies and platelets antigens form immune complexes, which result in platelets clearance by reticuloendothelial system. Viruses are capable of inducing expression of cryptic antigens through direct infection of the cells.

Management of coexisting conditions in patients with COVID-19 requires an individualized approach to achieve a precise balance between the risk of severe bleeding and thromboembolic events. Steroid treatment is the standard and most used first-line therapy for the management of newly diagnosed or relapsed ITP [9], [10]. Administration of steroid therapy increases the risk of viral infections and may lead to suppression of the immune system, but in patients with ITP who received steroids, no worsening of COVID-19 course or symptoms was reported. In patients with comorbidities, minimum effective dose and duration should be considered. Another first-line therapy for ITP is IVIG, which is more appropriate in cases with very low platelet counts and in patients at increased risk of severe bleeding. A practical guidance for the management of adults with ITP during the COVID-19 pandemic by Pavord *et al*. [11] recommends steroids as first-line treatment at minimum effective dose and duration and IVIG in two occasions: (1) First-line option in patients at risk for severe bleeding and (2) patients who failed first-line therapy with steroids.

Another hematologic autoimmune disorder seen in our patients with COVID-19 is AIHA, which is a rare autoimmune disorder characterized by the presence of autoantibodies that react with red blood cells and result in their destruction [12]. This disorder should mainly be suspected in patients with severe anemia and an abrupt decrease in hemoglobin concentration in a case when no other attributable causes can be identified. An AIHA was suspected in our cases due to symptomatic anemia, evidence of ongoing hemolysis on the blood tests, and a history of a viral infection. Hemolysis secondary to viral infections is a common finding [13].

Although the mechanism is not fully understood, there are theories that propose an autoimmune response by molecular simulation of host antigens by viral-derived peptides that cause cross-activation of autoreactive T or B cells. The strongest hypothesis for this phenomenon relies on the inflammatory context caused by SARS-CoV-2 infection. A cytokine-rich inflammatory environment alters the antigen presentation process by the antigen presenting cells witch results in a modified antigen repertoire presented to T lymphocytes, of which cryptic antigens may be a part. A second hypothesis is based on the existence of a shared epitope sequence between the SARS-CoV-2 spike protein and the ankyrin-1 protein present on the RBC membrane [14], [15], [16]. In most of the patients in this study, a rapid correction of the hemoglobin level was observed. A good response to corticosteroid therapy was noticed, except in two patients in need of additional immunosuppressive therapy.

Until now, only a few studies have presented data on the occurrence of TTP after SARS-CoV-2 infection with possible pathogenetic mechanisms. Most recently, Mancini *et al*. [17] have added to this data by evaluating the von Willebrand factor (VWF) – a disintegrin and metalloprotease with thrombospondin 1-domain (ADAMTS-13) axis. They found that median VWF levels markedly elevated and increased with intensity of care, and there was a relative increase of intermediate and low-molecular-weight VWF multimers in severe cases. The authors concluded that an elevated VWF antigen (VWF: Ag) to ADAMTS-13 activity ratio was strongly associated with disease severity. More data are needed to clarify the possible mechanisms for the consequent onset of TTP after viral injection [18], [19]. In our study, we observed a small number of patients with TTP, all of them were treated with standard therapeutic modalities such as plasmapheresis and corticosteroids with a good response similar to TTP caused by another etiological factor.

Conclusion

Causal relationship between SARS-CoV-2 infection and these autoimmune events requires further investigations. The risk of the development of hematologic autoimmune disorders in infected patients with COVID-19 should always be considered and an autoimmune etiology for cases with abnormal hematologic finding should be ruled out. This will contribute to an appropriate treatment and COVID-19 management. Therefore, the possibility of such events occurring should be taken into account, which requires constant monitoring of the patients. This will result in early physician's clinical suspicion and early measures when the manifestations of the autoimmune disorders first appear. Several reports of this condition in asymptomatic COVID-19 patients emphasize the need for COVID-19 testing in newly diagnosed patients with ITP, TTP, and AIHA amid this pandemic.

References

1. Kadkhoda K. COVID-19: An immunopathological view. mSphere. 2020;5(2):e00344-20. https://doi.org/10.1016/j.autrev.2020.102597
   PMid:32321823
2. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, Alijotas-Reig J, Zinserling V, Semenova N, Amital H, Shoenfeld Y. COVID-19 and autoimmunity. Autoimmun Rev. 2020;19(8):102597.
   PMid:32535093
3. Rodríguez Y, Novelli L, Rojas M, de Santis M, Acosta-Ampudia Y, Monsalve DM, *et al*. Autoinflammatory and autoimmune conditions at the crossroad of COVID-19. J Autoimmun. 2020;114:102506. https://doi.org/10.1016/j.jaut.2020.102506
   PMid:32563547
4. Zulfiqar AA, Orenzo-Villalba N, Hassler P, Andrès E. Immune thrombocytopenic purpura in a patient with COVID-19. N Engl J Med. 2020;382(18):e43. https://doi.org/10.1056/nejmc2010472
   PMid:32294340
5. Hindilerden F, Yonal-Hindilerden I, Akar E, Kart-Yasar K. COVID-19 associated autoimmune thrombotic thrombocytopenic purpura: Report of a case. Thromb Res. 2020;195:136-8. https://doi.org/10.1016/j.thromres.2020.07.005
   PMid:32688098
6. Hindilerden F, Yonal-Hindilerden I, Akar E, Yesilbag Z, Kart-Yasar K. Severe autoimmune hemolytic anemia in COVID-19 infection, safely treated with steroids. Mediterr J Hematol Infect Dis. 2020;12(1):e2020053. https://doi.org/10.4084/mjhid.2020.053
   PMid:32670531
7. Assinger A. Platelets and infection-an emerging role of platelets in viral infection. Front Immunol. 2014;5:649. https://doi.org/10.3389/fimmu.2014.00649
   PMid:25566260
8. Xu P, Zhou Q, Xu J. Mechanism of thrombocytopenia in COVID-19 patients. Ann Hematol. 2020;99(6):1205-8. https://doi.org/10.1007/s00277-020-04019-0
   PMid:32296910
9. Thachil J, Tang N, Gando S, Falanga A, Cattaneo M, Levi M, *et al*. ISTH interim guidance on recognition and management of coagulopathy in COVID-19. J Thromb Haemost. 2020;18(5):1023-6. https://doi.org/10.1111/jth.14810
   PMid:32338827
10. Tang KT, Hsu BC, Chen DY. Autoimmune and rheumatic manifestations associated with COVID-19 in adults: An updated systematic review. Front Immunol. 2021;12:645013. https://doi.org/10.3389/fimmu.2021.645013
    PMid:33777042
11. Pavord S, Thachil J, Hunt BJ, Murphy M, Lowe G, Laffan M, *et al*. Practical guidance for the management of adults with immune thrombocytopenia during the COVID-19 pandemic. Br J Haematol. 2020;189(6):1038-43. https://doi.org/10.1111/bjh.16775
    PMid:32374026
12. Lazarian G, Quinquenel A, Bellal M, Siavellis J, Jacquy C, Re D, *et al*. Autoimmunehemolyticanemia associated with COVID-19infection. Br J Haematol. 2020;190(1):29-31. https://doi.org/10.1111/bjh.16794
    PMid:32374906
13. Hill QA, Hill A, Berentsen S. Defining autoimmune hemolytic anemia: A systematic review of the terminology used for diagnosis and treatment. Blood Adv. 2019;3(12):1897-906. https://doi.org/10.1182/bloodadvances.2019000036
    PMid:31235526
14. Li Q, Cao Y, Chen L, Wu D, Yu J, Wang H, *et al*. Hematological features of persons with COVID-19. Leukemia. 2020;34(8):2163-72.
    PMid:32528042
15. Revuz S, Vernier N, Saadi L, Campagne J, Poussing S, Maurier F. Immune thrombocytopenic purpura in patients with COVID-19. Eur J Case Rep Intern Med. 2020;7(7):001751. https://doi.org/10.12890/2020_001751
    PMid:32665935
16. da Silva RL. Viral-associated thrombotic microangiopathies. Hematol Oncol Stem Cell Ther. 2011;4(2):51-9.
    PMid:21727765
17. Mancini I, Baronciani L, Artoni A, Colpani P, Biganzoli M, Cozzi G, *et al*. The ADAMTS13-von willebrand factor axis in COVID-19 patients. J Thromb Haemost. 2021;19(2):513-21. https://doi. org/10.1111/jth.15191
    PMid:33230904
18. Zheng, XL, Vesely SK, Cataland SR, Coppo P, Geldziler B, Iorio A, *et al*. ISTH guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020;18(10):2496-502. https://doi.org/10.1111/jth.15010
    PMid:32914526
19. Cohen MK, Sheena L, Shafir Y, Yahalom V, Gafter-Gvili A, Spectre G. An early unexpected immune thrombotic thrombocytopenic purpura relapse associated with SARS-CoV-2 infection: A case report and literature review. Acta Haematol. 2021;1-5. https://doi.org/10.1159/000514283
    PMid:33895748