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Coronavirus Pandemic

The evaluation of the relationship between COVID-19 and autoimmune responses with a cross-sectional trial using medical records

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Abstract

Introduction: Several previous studies have suggested a link between autoimmune activation and SARS-CoV-2 infection. This study aims to evaluate the excessive immune response via laboratory and radiological findings, treatment options, and previous acute phase reactants in patients with mild and moderate coronavirus disease 2019 (COVID-19) to identify the possible interaction between autoimmune response and SARS-CoV-2 infection.

Methodology: A total of 345 hospitalized patients with a diagnosis of definitive COVID-19 were evaluated retrospectively in terms of their clinical, laboratory, and radiological data, comorbidities, treatment options, and the values of C-reactive protein (CRP) of all patients in the last year before COVID-19 during admission to the hospital for any reason.

Results: 162 (47%) of the patients were female and 183 (53%) were male. The mean age was 51.08 ± 15.52 years. Of all patients, 235 (68.1%) had mild disease and 110 (31.9%) had a moderate disease. There was a statistically significant difference between the two groups in terms of age, gender, the values of leukocytes, lymphocytes, and hemoglobin, the levels of AST, LDH, Na, Cl, Ca, CRP, ferritin and fibrinogen, duration of hospitalization, medical treatments as well as the CRP value of the patients in the last year. Male gender, shortness of breath, duration of hospitalization, the value of lymphocytes, and the levels of LDH, CRP, and fibrinogen were independent predictive factors for the severity of COVID-19.

Conclusions: The SARS-CoV-2 infection could act as a triggering factor for developing autoimmune and/or autoinflammatory dysregulation in genetically predisposed individuals.

Key words: COVID-19; laboratory and radiological findings; treatment options; autoimmunity.

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Introduction

Coronavirus disease 2019 (COVID-19), which started in China and spread to many other countries in December 2019, has become a rapidly growing global epidemic that has been declared a pandemic by the World Health Organization (WHO) [1]. The virus is transmitted through respiratory droplets from coughs, sneezes, or direct contact. Although most patients remain asymptomatic, it causes pneumonia and acute respiratory distress syndrome (ARDS), which requires mechanical ventilation and hospitalization in the intensive care unit in 10-15% of cases, by infecting the respiratory tract in some patients. Patients usually present with fever, dry cough, dyspnoea, fatigue, headache, malaise, muscle and bone pain. Less common symptoms include sore throat, runny nose, confusion, sputum cough, hemoptysis, diarrhea, nausea, chest pain, and taste and smell disturbance. It enters the cell by binding to the angiotensin-converting enzyme (ACE) 2 receptor in the host cell membrane via the Spike (S) protein in the virus envelope. These ACE2 receptors are found in the airway (nasal) epithelium, lung alveoli, vascular endothelium, renal tubule cells, small intestine cells, and nerve cells in the body. This situation causes a wide clinical spectrum of the disease [2].

This virus can activate innate and adaptive immune responses, resulting in massive inflammatory responses later. The occurring uncontrolled inflammatory response may lead to local and systemic tissue damage. Normally, interferon released from virus-infected cells has an important role in eradicating the pathogen, while the Nucleocapsid (N) protein of the virus leads to remain a low level of interferon and releases a high level of proinflammatory cytokines such as interleukin (IL) -1, IL-6, and tumor necrosis factor (TNF)-α in COVID-19. Known as cytokine storm, this condition causes ARDS and multiple organ failures or even death in some virus-infected people [3].

Infectious agents have long been considered as one of the triggers for autoimmune and autoinflammatory diseases, mainly via promoting the production of autoantibodies and cytokines due to molecular mimicry. Other possible mechanisms proposed for the induction of autoimmunity are epitope spreading, bystander activation, auto-reactive T cells, and breaking immunological tolerance. Therefore, COVID-19 could act as a direct trigger of autoimmune and/or autoinflammatory responses in predisposed individuals.

Table 1. The demographic and clinical data, the initial laboratory findings and previous level of C-reactive protein (CRP) of the patients.

Variables	n = 345
Age	51.08 ± 15.52
Gender	
Female	47% (162)
Male	53% (183)
Smoking	
Smoker	38.6% (133)
Non-smoker	61.4% (212)
Duration of hospitalization (day)	7.44 ± 4.18
Symptoms	
Fever	49.3% (170)
Cough	77.7% (268)
Shortness of breath	50.4% (174)
Sore throat	8.7% (30)
Headache	6.7% (23)
Nausea or vomiting	5.5% (19)
Diarrhea	7% (24)
Arthralgia	2% (7)
Myalgia	11.9% (41)
Dorsal pain	5.5% (19)
Fatigue	27.8% (96)
Loss of taste	2.6% (9)
Loss of smell	3.2% (11)
Chronic diseases	
None	42.9% (148)
Hypertension	44.1% (152)
Diabetes mellitus	27.8% (96)
Hyperlipidemia	16.5% (57)
Coronary artery disease	7% (24)
Hypothyroidism	5.2% (18)
Chronic obstructive pulmonary disease	6.7% (23)
Chronic heart failure	1.4% (5)
Chronic kidney failure	2.3% (8)
Cerebrovascular event	2.6% (9)
Cancer	2.6% (9)
Others	2.3% (8)
Thorax CT findings	
Normal	4% (14)
Mild pneumonia	63.5% (219)
Moderate pneumonia	32.5% (112)
Treatment	
Hydroxychloroquine + azithromycin + oseltamivir	45.2% (156)
Favipiravir + prednisolone + different antibiotic drugs	47% (162)
Hydroxychloroquine + azithromycin + oseltamivir + favipiravir	4.6% (16)
Hydroxychloroquine + azithromycin+ oseltamivir + favipiravir + tocilizumab	0.6% (2)
Favipiravir + prednisolone + different antibiotic drugs + tocilizumab	2.6% (9)
Complete Blood Count findings	
Leukopenia	16.5% (57)
Leukocytosis	7.8% (27)
Lymphopenia	27% (93)
Thrombocytopenia	13.3% (46)
Thrombocytosis	7.8% (27)
Decreased hemoglobin	16.2% (56)
Blood Biochemistry findings	
Increased transaminase	29% (100)
Increased LDH	53.6% (185)
Increased amylase	10.7% (37)
Increased CK-MB	5.8% (20)
High ferritin	31.6% (109)
High fibrinogen	60.3% (208)
High D-dimer	49.3% (170)
High CRP	74.5% (257)
Decreased Na	27% (93)
Decreased Cl	36.2% (125)
Decreased Ca	22.9% (79)
The mean CRP value in the last year (0-0.5 mg/dL)	0.53 ± 0.38

All values are expressed as mean ± standard deviation, number, and percentage.

There are several studies to clearly define the possible interaction between SARS-CoV-2 infection and autoimmune disease onset such as autoimmune hemolytic anemia, immune thrombocytopenic purpura, autoimmune thyroid diseases, Kawasaki disease, Guillain-Barre syndrome (GBS), systemic lupus erythematosus (SLE) and the detection of autoantibodies. Also, recent studies have demonstrated that 10% to 15% of patients with critical COVID-19 pneumonia exhibit autoantibodies against type I interferons, suggesting that preexisting autoimmunity underlies severe disease in some patients [4-8]. In light of this information, this study aims to evaluate the excessive immune response via laboratory and radiological findings, treatment options, and previous acute phase reactants in patients with mild and moderate COVID-19 to identify the possible interaction between autoimmune response and SARS-CoV-2 infection.

Methodology

Study Design and participants

This single-centered, retrospective study was based on an analysis of the medical records of hospitalized patients with COVID-19 who applied to Kocaeli Government Hospital, Turkey between June 2020 and September 2020. The study protocol was approved by both the Ministry of Health and the Ethical Committee of Derince Training and Research Hospital (Trial Registration: DEAH GOKAEK 2020/129).

345 (162 female, 183 male) patients with a diagnosis of mild/moderate COVID-19 were included in this study. Male and nonpregnant female patients 18 years of age or older were contained. The patients who applied to Kocaeli Government Hospital between March 2020 and December 2020 were positive for the SARS-CoV-2 real-time reverse transcriptase-polymerase chain reaction (RT-PCR) test in the nasopharyngeal swab samples were collected retrospectively. None of the patients had a previous clinical record of autoimmune disease. Patients were classified into mild and moderate disease groups based on initial clinical presentation.

Data including age, sex, using smoke, chronic diseases (hypertension, diabetes mellitus, hyperlipidemia, hypothyroidism, coronary artery disease, chronic obstructive pulmonary disease, chronic kidney failure, chronic heart failure, cerebrovascular events), initial clinical symptoms, laboratory findings, and chest CT scan results at admission, duration of hospitalization, and applied drug treatments in all cases were obtained from previous electronic medical record

system. We also examined the values of CRP of all patients in the last year before COVID-19 during admission to the hospital for any reason. The most recent value was recorded if there was more than one CRP value.

Statistical analysis

All statistical analyses were performed using IBM SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY). The Kolmogorov-Smirnov and Shapiro-Wilk tests were used to assess the assumption of normality. Numerical variables were presented as mean ± standard deviation. Categorical variables were summarized as counts (percentages). Differences between groups were determined by independent-sample *t*-test for numerical variables with normal distribution and by Kruskal Wallis test for numerical variables without normal distribution. Relationships between categorical variables were evaluated using the Chi-square test or Fisher's Exact test. Dunn Bonferroni post-hoc test was used to determine from which group if there was a difference. The binary logistic regression Backward LR method was used to determine the cause-effect relationship between the dependent variable and the independent variables. The goodness of fit for logistic regression models was performed by the Hosmer-Lemeshow test. The likelihood-ratio statistic was used to compare the estimated models. A p value < 0.05 was considered statistically significant.

Results

Among the 345 patients, 162 (47%) of the patients were female and 183 (53%) were male. The mean age of the patients was 51.08 ± 15.52 years. The demographic and clinical characteristics, initial clinical symptoms, laboratory findings, duration of hospitalization, and drug treatments of patients are presented in Tables 1 and 2. There was a statistically

Table 2. The demographic and clinical characteristics, duration of hospitalization, medical treatments and the initial laboratory findings in the groups.

Variables	The patients with mild disease (n = 235)	The patients with moderate disease (n = 110)	*p* value
Age	47.43 ± 15.65	58.87 ± 12.04	**< 0.001**
Gender			
Female	29% (100)	18% (62)	**0.017**
Male	39.1% (135)	13.9% (48)	
Smoking			
Smoker	27.8% (96)	10.7% (37)	0.199
Non-smoker	40.3% (139)	21.2% (73)	
Duration of hospitalization (day)	6.37 ± 3.54	9.72 ± 4.53	**< 0.001**
Treatment			
Hydroxychloroquine + azithromycin + oseltamivir	39.4% (136)	5.8% (20)	**< 0.001**
Favipiravir + prednisolone + different antibiotic drugs	26.4% (91)	20.6% (71)	
Hydroxychloroquine + azithromycin+ oseltamivir + favipiravir	1.4% (5)	3.2% (11)	
Hydroxychloroquine + azithromycin + oseltamivir + favipiravir + tocilizumab	0.3% (1)	0.3% (1)	
Favipiravir + prednisolone + different antibiotic drugs + tocilizumab	0.6% (2)	2% (7)	
Complete Blood Count findings			
Leukocyte × 10^3 /L	5932.89 ± 2211.54	6608.99 ± 3150.65	**0.044**
Lymphocyte × 10^9 /L	1.46 ± 0.63	1.08 ± 0.49	**< 0.001**
Thrombocyte × 10^9 /L	215.98 ± 73.00	217.65 ± 106.42	0.882
Hemoglobin g/dL	13.66 ± 1.79	13.06 ± 1.88	**0.004**
AST (0-50 U/L)	34.60 ± 20.67	43.97 ± 23.05	**< 0.001**
ALT (0-55 U/L)	30.53 ± 21.24	33.16 ± 22.68	0.294
LDH (0-248 U//L)	241.38 ± 79.00	337.76 ± 141.38	**< 0.001**
Amylase (28-100 U/L)	68.66 ± 31.29	65.37 ± 34.07	0.378
CK-MB (0-24 U/L)	14.97 ± 6.99	16.82 ± 15.12	0.122
Na (136-146 mEq/dL)	137.56 ± 4.26	136.09 ± 3.68	**0.002**
Cl (101-109 mEq/dL)	101.63 ± 6.92	99.73 ± 3.62	**0.007**
Ca (8.6-10.6 mg/dL)	9.12 ± 0.69	8.74 ± 0.50	**< 0.001**
Ferritin (21.81-274.66 mg/dL)	192.77 ± 167.64	428.68 ± 443.82	**< 0.001**
Fibrinogen (200-400 mg/dL)	394.88 ± 148.35	558.86 ± 147.19	**< 0.001**
D-dimer (0-0.5 ug/mL)	1.21 ± 8.75	0.94 ± 0.70	0.742
CRP (0-0.5 mg/dL)	2.62 ± 4.06	9.38 ± 6.97	**< 0.001**
CRP in last year	0.50 ± 0.39	0.60 ± 0.36	**0.014**

$p < 0.05$: significant difference; p values were calculated by independent-sample t-test; Chi-square test or Fisher's Exact test.

significant difference between the two groups in terms of age, gender, the values of leukocytes, lymphocytes, and hemoglobin, the levels of AST, LDH, Na, Cl, Ca, CRP, ferritin and fibrinogen, duration of hospitalization, medical treatments. Also, there was a statistically significant difference between the two groups in terms of the CRP value of the patients in the last year (Table 2). There was a statistically significant difference between the two groups regarding cough, shortness of breath, sore throat, headache, and myalgia (Table 3). There was a statistically significant difference between the two groups regarding HT, DM, and cancer (Table 3). Male gender, shortness of breath, duration of hospitalization, the value of lymphocytes, and the levels of LDH, CRP, and fibrinogen were identified as independent predictive factors for the severity of COVID-19 (Table 4).

Discussion

Several previous studies have suggested a link between autoimmune activation and COVID-19 [4,5]. Therefore, we assessed the laboratory and radiological findings, treatment outcomes, and previous levels of CRP in mild and moderate COVID-19 patients to understand how autoimmunity may be affected by SARS-CoV-2 infection. We also defined risk factors linked to the severity of the disease. There was a statistically significant difference between the two groups in terms of age, gender, the values of leukocytes, lymphocytes, and hemoglobin, the levels of AST, LDH, Na, Cl, Ca, CRP, ferritin and fibrinogen, duration of hospitalization, medical treatments as well as the CRP value of the patients in the last year. Older age, male gender, increased values of leukocytes, decreased values of lymphocytes and hemoglobin, increased levels of AST, LDH, CRP, ferritin, and fibrinogen, decreased levels of Na, Cl, and Ca at admission were significantly associated with the severity of disease condition. Moreover, male gender, shortness of breath, duration of hospitalization, the value of lymphocyte, and the levels of LDH, CRP, and fibrinogen were

Table 3. The initial symptoms and the presence of chronic diseases in groups.

Variables	Patients with mild disease (n = 235)	Patients with moderate disease (n = 110)	*p* value
Symptoms			
Fever	33.3% (115)	15.9% (55)	0.854
Cough	48.7% (168)	29% (100)	**< 0.001**
Shortness of breath	28.4% (98)	22% (76)	**< 0.001**
Sore throat	8.1% (28)	0.6% (2)	**0.002**
Headache	5.8% (20)	0.9% (3)	**0.045**
Nausea or vomiting	4.3% (15)	1.2% (4)	0.297
Diarrhea	5.8% (20)	1.2% (4)	0.097
Arthralgia	1.7% (6)	0.3% (1)	0.438
Myalgia	10.1% (35)	1.7% (6)	**0.012**
Dorsal pain	4.6% (16)	0.9% (3)	0.121
Fatigue	20% (69)	7.8% (27)	0.352
Loss of taste	2% (7)	0.6% (2)	0.724
Loss of smell	2.6% (9)	0.6% (2)	0.513
Diseases			
Hypertension	24.9% (86)	19.1% (66)	**< 0.001**
Diabetes mellitus	14.2% (49)	13.6% (47)	**< 0.001**
Hyperlipidemia	9.9% (34)	6.7% (23)	0.133
Coronary artery disease	4.3% (15)	2.6% (9)	0.541
Hypothyroidism	3.2% (11)	2% (7)	0.512
COPD	3.5% (12)	3.2% (11)	0.089
Chronic heart failure	0.6% (2)	0.9% (3)	0.332
Chronic renal failure	0.9% (3)	1.4% (5)	0.116
Cerebrovascular event	1.2% (4)	1.4% (5)	0.151
Cancer (CA)	0.6% (2)	2% (7)	
Breast CA	0.3% (1)	0.3% (1)	
Lung CA	0% (0)	0.3% (1)	
Kidney CA	0% (0)	0.3% (1)	
Colon CA	0% (0)	0.3% (1)	**0.006**
Bladder CA	0% (0)	0.3% (1)	
Thyroid CA	0% (0)	0.3% (1)	
Brain CA	0% (0)	0.3% (1)	
Multiple myeloma	0.3% (1)	0% (0)	

$p < 0.05$: significant difference; COPD: Chronic obstructive pulmonary disease; *p* values were calculated by Chi-square test or Fisher's Exact test.

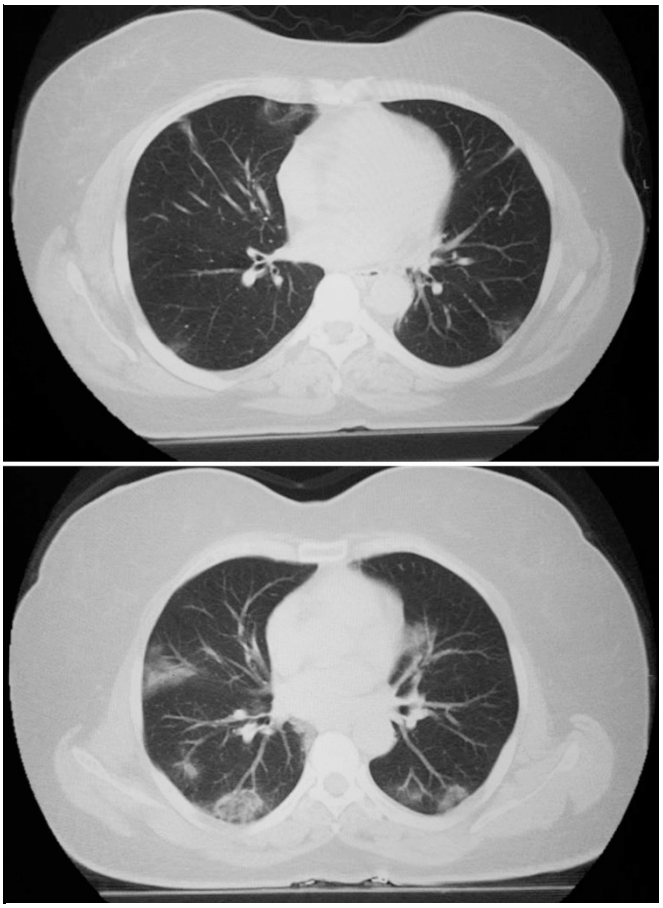
identified as independent predictive factors for the severity of COVID-19.

The average age of the patients included in our study was 51 years old and 53% of patients were male. The Spike protein is responsible for the attachment of the viral particle to target cells that express its ligand, the ACE-2 receptor on their surface [9]. A second target cell membrane component is Transmembrane protease, serine 2 (TMPRSS-2), a type II transmembrane protease that cleaves and activates the Spike protein. The fact that TMPRSS-2 is an androgen-controlled protease, previously linked to translocation in prostate cancer, could offer an explanation for the male bias of COVID-19 disease [10].

The inflammatory status of the patients with COVID-19 was evaluated considering the common diagnostic inflammatory markers: LDH, CRP, ferritin, the number of lymphocytes, and hemoglobin. In our study, 27% of patients had lymphopenia and 16.2% of patients had decreased hemoglobin. It was found that the CRP level increased by 74.5%, the ferritin level increased by 31.6%, the fibrinogen level increased by 60.3% and the level of LDH increased in 53.6% of patients. Another way of entering SARS-CoV-2 into the cell may be antibody-dependent augmentation (ADE). In the presence of anti-S antibodies, the virus enters cells with the Fc-γ-2 (CD32) receptor on its surface in the form of an antibody-virus complex and may subsequently exert a cytopathic effect [11]. ADE phenomenon may be responsible for the occurrence of lymphopenia. Other hypothetical explanations for lymphopenia in COVID-19 patients are a) lymphocyte death and damage to lymphoid organs as a result of virus binding to ACE2 receptors on the lymphocyte surface, b) lymphocyte apoptosis due to cytokine storm, and c) lymphocyte homing from peripheral blood into tissue [7,12]. ACE2 is especially a type 1 transmembrane aminopeptidase expressed in the heart and lungs. Therefore, COVID-19 potentially causes lung and acute myocardial injury [12]. In our study, increased CK-MB was observed in only 5.8% of the patients. We also found increased transaminases in 29%, increased amylase in 10.7%, decreased Na in 27%, decreased Cl in 36.2%, and decreased Ca in 22.9% of the patients. ACE2 receptors are also said to be present in the liver, digestive organs, and kidneys. These tissues and organs could thus be potential targets for SARS-CoV-2 invasion. This explains why many patients with COVID-19 present with extrapulmonary symptoms [13].

Wang *et al.* categorized the pulmonary imaging of patients with COVID-19 into three groups including small patchy opacities (mild), large ground-glass opacity (moderate), and largely consolidated opacity (severe) [14]. In our study, thoracic CT findings showed

Figure 1. The radiologic images of patients with mild and moderate COVID-19.



Top: mild pneumonia; **Bottom:** moderate pneumonia).

Table 4. Logistic regression modelling evaluating independent predictive factors of severity of disease in COVID-19.

Variables	B (Odds ratio)	*p* value	95% CI for B
Gender (Male)	1.022	0.018	0.998-1.047
Shortness of breath	1.390	0.045	1.008-1.916
Duration of hospitalization	1.150	0.001	1.062-1.246
The value of lymphocyte	1.003	0.029	1.000-1.000
The level of LDH	1.006	0.003	1.002-1.010
The level of CRP	1.156	< 0.001	1.071-1.247
The level of fibrinogen	1.003	0.029	1.000-1.006

$p < 0.05$, significant difference, CI: Confidence interval.

normal in 4% of the patients, mild pneumonia in 63.5%, and moderate pneumonia in 32.5% (Figure 1). It seems that the radiological aspects of lung involvement in patients with COVID-19 resemble findings characterizing pneumonia of autoimmune diseases (i.e., rheumatoid arthritis, systemic sclerosis, and eosinophilic granulomatosis with polyangiitis), and autoinflammatory diseases (i.e., systemic juvenile idiopathic arthritis).

The proposed pathophysiological mechanisms are different in all stages of the disease, an increase in viral replication is at the forefront in the mild stage (Stage 1, early infection) and the first stage of the middle stage (Stage 2a, pulmonary involvement without hypoxia) whereas hyper inflammation is prominent in the second stage of the middle stage (Stage 2b, pulmonary involvement with hypoxia) and the severe stage (Stage 3, systemic hyper inflammation and cytokine storm) [15]. Therapeutic approaches to COVID-19 treatment include the use of antiviral agents that interfere with the SARS-CoV-2 life cycle to prevent further viral replication, and the use of immunomodulators and anti-inflammatory agents to reduce the immune system to prevent cytokine storm and tissue damage [16]. Azithromycin alone or combined with hydroxychloroquine could reduce the need for hospitalization or time to clinical recovery in stage 1 but not in stages 2 and 3. Immunomodulatory therapies such as corticosteroids and tocilizumab would be required in the later stage of the treatment of COVID-19 [17]. Although patients with severe lung involvement and/or in need of an intensive care unit were not included in our study, the discharge of all our patients to recovery has been associated with the combined use of antiviral (oseltamivir and/or favipiravir) and anti-inflammatory (hydroxychloroquine, methylprednisolone, and tocilizumab) drug therapies in the patients without lung involvement or with mild/moderate lung involvement. This explains why the drugs used to treat autoimmune diseases are useful in the treatment of COVID-19. No side effects were observed in patients related to drug treatment in our study.

Additionally, selecting the drugs to be used in the second stage and the starting time are critical [18]. Pongpirul *et al.* reported that the median time from the onset of illness to pneumonia detection was 7.0 (5.0-9.0) days [19]. Chen *et al.* suggested that the disease progressed as evidenced by radiological worsening within 7 days after the onset of symptoms and persistent fever, lung injury and disease progression can be partly explained by uncontrolled viral replication [20]. Zhou *et al.* reported that patients developed sepsis on the 9th day of disease onset and ARDS on the 10th day [21]. Corominas et al. proposed that IL-6 receptor blockers such as tocilizumab, sarilumab, and siltuximab can be successful in the treatment of moderate and severe patients and instead of waiting for the disease to progress too much, more successful results may be obtained by administering drugs, especially at the early stages of cytokine release syndrome [22]. Better recovery and a shorter duration of hospitalization were achieved with the combination of azithromycin, hydroxychloroquine, and oseltamivir initiated at an early stage in our study. Moreover, we observed that administering tocilizumab at an early stage may reduce the need for an intensive care unit and death when the blood picture of the patients deteriorates despite initial treatment. The most critical molecule in cytokine storm is IL-6, which is released from activated macrophages and monocytes. It both activates the JAK/STAT pathway and increases Th17 differentiation. Also, IL-6 increases the release of CRP, fibrinogen, and ferritin from the liver [23]. It has been shown that there is a significant increase in this cytokine level in patients with severe disease progression and that high IL-6 level contributes to the formation of the cytokine storm [24]. This explains both their increased acute phase reactants in the blood of patients and the useful effect of tocilizumab, acting as an IL-6 monoclonal antagonist, in clinical improvement in severe COVID-19 pneumonia.

The heterogeneity and multiplicity of the disorders caused by COVID-19 may result from the phenomenon of molecular mimicry between virus and human proteins due to the high sharing of peptides between the human proteome and the viral spike glycoprotein. The molecular mimicry could lead to the synthesis of multiple autoantibodies, causing a trigger effect of possibly pre-existing autoimmune disease and resulting in the new onset of an autoimmune disease. These autoantibodies result in organ-specific (e.g., GBS) or systemic (e.g., SLE) autoimmunity. Initially, infection of SARS-CoV-2 via the ACE2 receptor reduces the production of IFN, with a paradoxical increased secretion of chemokines which stimulates the migration of innate immune cells to the lungs in the early stages of the disease. Subsequently, the migration of T and B cells induced by chemokines promotes an increase of Th1/Th17 cytokines that perpetuate inflammation. The virus leads to the induction of danger signals via activating Toll-like receptor and dysregulated NOD-like receptor 3 inflammasome which promotes the release of IL-1β, IL-18, and IL-33 and Th1 polarization,

with subsequent TNFα and IL-6 production. Naturel killer (NK) and Th1 cells stimulated by IL-1β, IL-18, and IL-33 the production of IFN-γ and monocyte chemotactic protein (MCP)-1. These chemokines cause the recruitment of leukocytes (such as neutrophils and macrophages) to the sites of infection. In addition, IL-1β and TNF-α released from inflammatory cells support Th17 responses. Along with Th1, the Th17-type response contributes to the production of high levels of proinflammatory cytokines, termed the cytokine storm syndrome (CSS). IL-6 plays a central role in CSS, activating the coagulation pathway and vascular endothelial cells, inhibiting myocardial function, and inducing Th17 differentiation, resulting in increased pro-inflammatory activity. Also, IL-6 increases the release of CRP, fibrinogen, and ferritin from the liver. A pro-inflammatory milieu including the presence of IL-6 and IL-1β may decrease cytolytic functions of NK cells and CD8+ T cells, resulting in a reduced ability to lyse active antigen-presenting cells or infected cells. This leads to macrophage activation, hemophagocytosis, and multi-organ failure. Moreover, neutrophils are thought to produce NETosis which may help to increase inflammation and produce the release of cryptic antigens leading to autoimmune phenomenon [5-7,25-27].

NETosis, known as NETs activation and release, is a beneficial antimicrobial mechanism of neutrophils that intervenes by capturing and killing invading pathogens to minimize damage to host cells. NETs are networks of extracellular fibers composed primarily of DNA and chromatin excreted from neutrophils and binding pathogens. However, NETs can also serve as a source of self-antigens leading to autoimmune conditions. NET-derived neutrophil proteases such as elastase can cause the release of peptidyl arginine deiminases (PADs) that increase citrullination of self-proteins (e.g., histones, cartilage proteins, others), making them autoreactive and promoting the pathogenic inflammatory cascade in autoinflammatory diseases. It has been demonstrated that the hemocytological change is neutrophilia and associated excess NETs that parallel lung injury in severe COVID-19 patients. The NET formation has also been associated with thrombosis. Similar to autoimmune diseases, damage-associated molecular models (DAMPs) also play a role in the pathogenesis of COVID-19. Overproduction and release of proinflammatory cytokines and chemokines can cause severe organ damage, which is also seen in autoimmune diseases in critical situations [5,12,25].

On the other hand, there are some limitations such as small sample size compared to the rest of the country, the absence of patients with severe lung involvement and/or in need of intensive care unit, the lack of pediatric or adolescent patients, the absence of IL-6 levels and autoantibodies titers in the present study. The level of IL-6 and autoantibodies could not be examined because it could not be performed in our hospital laboratory. However, there was a statistically significant difference between the mild and moderate groups in terms of the previous CRP value of the patients. According to the results of our study, those with high pre-illness CRP values seem to be clinically more affected.

Conclusions

The autoimmune response could explain the lack of clinical improvement or a long recovery despite the resolution of the viral infection in some cases. The correlation between the response to SARS-CoV-2 and the specific individual autoimmune response could be the reason for the wide variability of clinical manifestations related to a single pathogen. In addition, the autoimmune response that occurs in COVID-19 patients may vary according to disease stage. The dysregulated immune response and increased pro-inflammatory cytokines induced by SARS-CoV-2 contribute to the disease pathogenesis and organ damage. The described clinical conditions and laboratory tests indicate the hyper-stimulated state of the immune system which plays an important role in the severity of the disease and the death of patients. Also, the characteristic lymphopenia in patients with COVID-19 may lead to failure in the maintenance of peripheral tolerance (or loss of self-tolerance), resulting in activation of effector T cells with autoimmune potential [4,5].

It seems that any factor that causes chronic inflammation in the body can potentially induce autoinflammatory/autoimmune diseases. Since the genetic background is considered one of the determining factors in the induction of autoimmunity, the characteristics of the host may also be important in making the disease persistent and pathogenic. Environmental factors may trigger or exacerbate an aberrant innate and acquired immune response, with the massive synthesis of cytokines in genetically susceptible subjects. As a result, SARS-CoV-2 could act as a triggering factor for the development of rapid autoimmune and/or autoinflammatory dysregulation in genetically predisposed individuals [7]. Moreover, understanding the effect of SARS-CoV-2 infection on

the body may lead to the chance of using this condition in the treatment of autoinflammatory/autoimmune diseases in the future. This way, a situation that is detrimental to humanity may be turned into an opportunity.

References

1. Puca E, Čivljak R, Arapović J, Popescu C, Christova I, Raka L, Cana F, Miranović V, Karageorgopoulos D, Baš D, Paglietti B, Barać A (2020) Short epidemiological overview of the current situation on COVID-19 pandemic in Southeast European (SEE) countries. J Infect Dev Ctries 14: 433-437. doi: 10.3855/jidc.12814.
2. García LF (2020) Immune response, inflammation, and the clinical spectrum of COVID-19. Front Immunol 11: 1441. doi: 10.3389/fimmu.2020.01441.
3. Ragab D, Eldin HS, Taeimah M, Khattab R, Salem R (2020) The COVID-19 cytokine storm; what we know so far. Front Immunol 11: 1446. doi: 10.3389/fimmu.2020.01446.
4. Sacchi MC, Tamiazzo S, Stobbione P, Agatea L, De Gaspari P, Stecca A, Lauritano EC, Roveta A, Tozzoli R, Guaschino R, Bonometti R (2021) SARS-CoV-2 infection as a trigger of autoimmune response. Clin Transl Sci 14: 898-907. doi: 10.1111/cts.12953.
5. Knight JS, Caricchio R, Casanova JL, Combes AJ, Diamond B, Fox SE, Hanauer DA, James JA, Kanthi Y, Ladd V, Mehta P, Ring AM, Sanz I, Selmi C, Tracy RP, Utz PJ, Wagner CA, Wang JY, McCune WJ (2021) The intersection of COVID-19 and autoimmunity. J Clin Invest 131: e154886. doi: 10.1172/JCI154886.
6. Ehrenfeld M, Tincani A, Andreoli L, Cattalini M, Greenbaum A, Kanduc D, Alijotas-Reig J, Zinserling V, Semenova N, Amital H, Shoenfeld Y (2020) Covid-19 and autoimmunity. Autoimmun Rev 19: 102597. doi: 10.1016/j.autrev.2020.102597.
7. Rodríguez Y, Novelli L, Rojas M, De Santis M, Acosta-Ampudia Y, Monsalve DM, Ramírez-Santana C, Costanzo A, Ridgway WM, Ansari AA, Gershwin ME, Selmi C, Anaya JM (2020) Autoinflammatory and autoimmune conditions at crossroad of COVID-19. J Autoimmun 114: 102506. doi: 10.1016/j.jaut.2020.102506.
8. Winchester N, Calabrese C, Calabrese LH (2021) The Intersection of COVID-19 and Autoimmunity: What is Our Current Understanding? Pathog Immun 6: 31-54. doi: 10.20411/pai.v6i1.417.
9. Walls AC, Park YJ, Tortorici MA, Wall A, McGuire AT, Veesler D (2020) Structure, Function, and Antigenicity of the SARS-CoV-2 Spike Glycoprotein. Cell 181: 281-292. doi: 10.1016/j.cell.2020.02.058.
10. Hoffmann M, Kleine-Weber H, Schroeder S, Krüger N, Herrler T, Erichsen S, Schiergens TS, Herrler G, Wu NH, Nitsche A, Müller MA, Drosten C, Pöhlmann S (2020) SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically proven protease inhibitor. Cell 181: 271-280. doi: 10.1016/j.cell.2020.02.052.
11. Yip MS, Leung HL, Li PH, Cheung CY, Dutry I, Li D, Daëron M, Bruzzone R, Peiris JS, Jaume M (2016) Antibody-dependent enhancement of SARS coronavirus infection and its role in the pathogenesis of SARS. Hong Kong Med J 22: 25-31.
12. Liu Y, Sawalha AH, Lu Q (2021) COVID-19 and autoimmune diseases. Curr Opin Rheumatol 33: 155-162. doi: 10.1097/BOR.0000000000000776.
13. Chakraborty R, Parvez S (2020) COVID-19: An overview of the current pharmacological interventions, vaccines, and clinical trials. Biochem Pharmacol. 2020; 180: 114184. doi: 10.1016/j.bcp.2020.114184.
14. Wang X, Fang J, Zhu Y, Chen L, Ding F, Zhou R, Ge L, Wang F, Chen Q, Zhang Y, Zhao Q (2020) Clinical characteristics of non-critically ill patients with novel coronavirus infection (COVID-19) in a Fangcang Hospital. Clin Microbiol Infect 26: 1063-1068. doi: 10.1016/j.cmi.2020.03.032.
15. Siddiqi HK, Mehra MR (2020) COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant 39: 405-407. doi: 10.1016/j.healun.2020.03.012.
16. Grifoni A, Sidney J, Zhang Y, Scheuermann RH, Peters B, Sette A (2020) A sequence homology and bioinformatic approach can predict candidate targets for immune responses to SARSCoV-2. Cell Host Microbe 27: 671-680. doi: 10.1016/j.chom.2020.03.002.
17. Echeverría-Esnal D, Martin-Ontiyuelo C, Navarrete-Rouco ME, De-Antonio Cuscó M, Ferrández O, Horcajada JP, Grau S (2021) Azithromycin in the treatment of COVID-19: a review. Expert Rev Anti Infect Ther 9: 147-163. doi: 10.1080/14787210.2020.1813024.
18. Wang Z, Yang B, Li Q, Wen L, Zhang R (2020) Clinical features of 69 cases with coronavirus disease 2019 in Wuhan, China. Clin Infect Dis 71: 769-777. doi: 10.1093/cid/ciaa225.
19. Pongpirul WA, Mott JA, Woodring JV, Uyeki TM, MacArthur JR, Vachiraphan A, Uttayamakul S, Pongpirul K, Manosuthi W, Prasithsirikul W (2020) Clinical course and potential predictive factors for pneumonia of adult patients with Coronavirus Disease 2019 (COVID-19): A retrospective observational analysis of 193 confirmed cases in Thailand. Emerg Infect Dis 26: 1580-1585. doi: 10.3201/eid2607.200598.
20. Chen J, Qi T, Liu L, Ling Y, Qian Z, Li T, Li F, Xu Q, Zhang Y, Xu S, Song Z, Zeng Y, Shen Y, Shi Y, Zhu T, Lu H (2020) Clinical progression of patients with COVID-19 in Shanghai, China. J Infect 80: e1-e6. doi: 10.1016/j.jinf.2020.03.004.
21. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, Xiang J, Wang Y, Song B, Gu X, Guan L, Wei Y, Li H, Wu X, Xu J, Tu S, Zhang Y, Chen H, Cao B (2020) Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. Lancet 395: 1054-1062. doi: 10.1016/S0140-6736(20)30566-3.
22. Corominas H, Castellví I, Domingo P, Casademont J (2020) Facing the SARS-CoV-2 (COVID-19) outbreak with IL-6R antagonists. Eur J Rheumatol 7: S107-S109. doi: 10.5152/eurjrheum.2020.20061.
23. Moore JB, June CH (2020) Cytokine release syndrome in severe COVID-19. Science 368: 473-474. doi: 10.1126/science.abb8925.
24. Anka AU, Tahir MI, Abubakar SD, Alsabbagh M, Zian Z, Hamedifar H, Sabzevari A, Azizi G (2021) Coronavirus disease 2019 (COVID-19): An overview of the immunopathology, serological diagnosis and management. Scand J Immunol 93: e12998. doi: 10.1111/sji.12998.
25. Dotan A, Muller S, Kanduc D, David P, Halpert G, Shoenfeld Y (2021) The SARS-CoV-2 as an instrumental trigger of autoimmunity. Autoimmun Rev 20: 102792. doi: 10.1016/j.autrev.2021.102792.

26. Sacchi MC, Tamiazzo S, Stobbione P, Agatea L, De Gaspari P, Stecca A, Lauritano EC, Roveta A, Tozzoli R, Guaschino R, Bonometti R (2021) SARS-CoV-2 infection as a trigger of autoimmune response. Clin Transl Sci 14: 898-907. doi: 10.1111/cts.12953.
27. Birra D, Benucci M, Landolfi L, Merchionda A, Loi G, Amato P, Licata G, Quartuccio L, Triggiani M, Moscato P (2020) COVID 19: a clue from innate immunity. Immunol Res 68: 161-168. doi: 10.1007/s12026-020-09137-5.

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