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Maculopapular Eruption in COVID-19 Patients: A Single-Center Comparative Study

COVID-19 Hastalarında Makulopapüler Erüpsiyon: Tek Merkezli Karşılaştırmalı Çalışma

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ABSTRACT

Aim: Maculopapular eruption (MPE) due to the coronavirus disease 2019 (COVID-19) is increasingly reported. This study aimed to evaluate COVID-19 patients presenting with MPE and compare them with COVID-19 patients without MPE.

Materials and Methods: COVID-19 patients with and without MPE followed up in a single tertiary center between March 2020 and December 2020 were assessed and compared in terms of demographic characteristics, clinical and laboratory findings.

Results: A total of 114 COVID-19 patients (female: male ratio=0.4: 1, mean age: 51.44±16.62 years) confirmed by total polymerase chain reaction testing were evaluated. Patients with MPE during COVID-19 (n=44) and patients without MPE during COVID-19 (n= 70) were divided into two groups and compared. Among clinical findings, the incidence of fever, myalgia, anosmi and ageusia, rhinorrhea, and/or nasal congestion was significantly higher in COVID-19 patients with MPE. In terms of laboratory findings, creatinine, alkaline phosphatase (ALP), gamma-glutamyl transferase, lactate dehydrogenase, vitamin D, erythrocyte sedimentation rate, procalcitonin, ferritin, fibrinogen median levels were significantly higher in COVID-19 patients with MPE. In complete blood count, median hemoglobin, red blood cell, monocyte, eosinophil, and basophil counts were also significantly higher in the MPE group. In the multivariate logistic regression model, ALP was independently associated with MPE in COVID-19 patients (odds ratio: 1.099, 95% confidence interval: 1.056-1.144, p<0.00).

Conclusion: The MPE in COVID-19 patients may be indicative of increased inflammation and organ damage. Early diagnosis and isolation of these patients and close follow-up are crucial in reducing the risk of organ damage and severe disease. In addition, ALP is an important laboratory parameter related to MPE in COVID-19 patients.

Keywords: Ageusia, anosmia, alkaline phosphatase, COVID-19, maculopapular eruption

ÖZ

Amaç: Koronavirüs hastalığı 2019 (COVID-19) nedeniyle oluşan makulopapüler erüpsiyon (MPE) giderek daha fazla bildirilmektedir. Bu çalışma, MPE ile başvuran COVID-19 hastalarını değerlendirmeyi ve MPE gelişimi görülmeyen COVID-19 hastalarıyla karşılaştırmayı amaçlamaktadır.

Gereç ve Yöntem: Mart 2020 ile Aralık 2020 arasında üçüncü basamak bir sağlık kuruluşunda takip edilen MPE'li ve MPE'siz COVID-19 hastaları demografik özellikler, klinik ve laboratuvar bulguları açısından değerlendirildi ve karşılaştırıldı.

Bulgular: Polimeraz zincir reaksiyonu testi ile doğrulanan toplam 114 COVID-19 hastası (kadın: erkek oranı=0,4: 1, ortalama yaş: 51,44±16,62 yıl) değerlendirildi. COVID-19 sırasında MPE görülen hastalar (n=44) ve COVID-19 sırasında MPE görülmeyen hastalar (n=70) iki gruba ayrılarak karşılaştırıldı. Klinik bulgular açısından ateş, miyalji, anosmi ve agezi, rinore ve/veya burun tıkanıklığı insidansı ve laboratuvar bulguları arasında; kreatinin, alkalen fosfataz (ALP), gama-glutamil transferaz, laktat dehidrogenaz, D vitamini, eritrosit sedimantasyon hızı, prokalsitonin, ferritin, fibrinojen MPE'li COVID-19 hastalarında anlamlı derecede daha yüksekti. Hemogram parametrelerinden de hemoglobin, kırmızı kan hücresi, monosit,

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eozinofil ve bazofil sayımlarının medyanı, MPE'li grupta anlamlı derecede daha yüksekti. Çok değişkenli lojistik regresyon modelinde, ALP COVID-19 hastalarında MPE ile bağımsız olarak ilişkiliydi (olasılık oranı: 1,099, %95 güven aralığı: 1,056-1,144, p<0,00).

Sonuç: COVID-19 hastalarında MPE, artmış enflamasyon ve organ hasarının göstergesi olabilir. Bu hastaların erken tanısı ve izolasyonu, yakın takibi organ hasarı ve ciddi hastalık riskini azaltmada çok önemlidir. Ayrıca, ALP COVID-19 hastalarında MPE ile ilişkili önemli bir laboratuvar parametresidir.

Anahtar Kelimeler: Agezi, anosmi, alkalen fosfataz, COVID-19, makülopapüler döküntü

INTRODUCTION

The coronavirus disease 2019 (COVID-19) is a highly contagious respiratory infection caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). The most common symptoms are fever, myalgia, malaise, sore throat, rhinorrhea and/or nasal congestion, cough, and dyspnea. However, apart from these typical symptoms, many symptoms related to neurological, gastrointestinal, and cardiovascular system involvement might be seen in the course of COVID-19[1].

Current literature has shown that 2-21% of COVID-19 patients may have dermatological manifestations. In the literature, it has been reported that lesions usually start with or occur after other symptoms of COVID-19, but there are also studies reporting that the rash appears 2-3 days before the onset of symptoms[2,3]. In a study of 11,544 people, the authors reported that 17% of SARS-CoV-2 patients had skin manifestations as the first symptom, and in 21%, skin manifestations were the only clinical evidence of the disease[3]. In this context, it is essential to know the dermatological findings well for early diagnosis and prevention of disease spread.

To date, many dermatologic involvements that may develop due to COVID-19 have been described. The most common ones are chilblain-like eruption, maculopapular eruption (MPE), urticarial lesions, vascular lesions (acro ischemia, livedo reticularis), and papulovesicular lesions. MPE is one of the most common dermatological involvements due to COVID-19. MPE might occur during viral infections and has two primary triggers: drugs and immune response to viral nucleotides. The absence of suspected drug use in the anamnesis is the most critical determinant of MPE due to viral nucleotides. However, it is not clear why MPE does not occur in every patient[2,3].

This study aimed to compare the demographic and clinical features and laboratory findings of COVID-19 patients according to the presence of MPE triggered by SARS-CoV-2 viral nucleotides.

MATERIALS AND METHODS

This retrospective comparative study assessed COVID-19 patients with MPE followed up in our single tertiary center. Patients under 18 years of age, patients with MPE following the initiation of any recent medication, and those with dermatological involvement other than MPE were excluded. Since we could not perform mutation analysis in our study, we also excluded patients diagnosed with COVID-19 after December 2020 in order not to evaluate patients with possible different mutations. COVID-19 patients without MPE development, diagnosed in the same period (between March 2020 and December 2020), were also included as a control group. The COVID-19 diagnosis was confirmed with polymerase chain reaction (PCR) testing in all patients.

The medical files of the patients were evaluated regarding demographic characteristics (age, sex), medical history (comorbidities, smoking status), clinical features (presence of fever, myalgia, dyspnea, sore throat, rhinorrhea and/or nasal congestion, diarrhea, nausea/vomiting, anosmia, ageusia, and cardiological symptoms), presence and degree of pulmonary involvement on computed tomography, and laboratory findings.

Differential blood count was performed on Mindray BC 6200 automatic complete blood count analyzer (Mindray Bio-Medical Electronics, Shenzhen, China). Prothrombin time, fibrinogen, and D-dimer levels were measured on ACL TOP 500 coagulation autoanalyzer (Instrumentation Laboratory, Bedford, MA). Erythrocyte sedimentation rate (ESR) was performed using the modified Westergren method on Vision C ESR analyzer (YHLO Biotech, Shenzhen, China). Serum procalcitonin and ferritin levels were quantified on cobas e601 immunanalyzer (Roche Diagnostics, Ma4nnheim, Germany) with the method of the electrochemiluminescent immunoassay. C-reactive protein was measured on IMMAGE 800 nephelometer (Beckman Coulter, Miami, FL). Serum glucose, alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), total bilirubin, direct bilirubin, creatinine (Cr), blood urea nitrogen, uric acid, albumin, magnesium, and calcium were performed on cobas c702 autoanalyzer (Roche Diagnostics, Mannheim, Germany) by using colorimetric and enzymatic methods.

Ethical approval was received from the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (decision no: 2022/15-05, date: 30.11.2022).

Statistical Analysis

The Kolmogorov-Smirnov test was used to verify the normality of the distribution of continuous variables, and data were expressed as mean ± SD or median (min.-max.) in the presence of abnormal distribution, and categorical variables as percentages. Comparisons between the groups of patients were made by using the chi-square or Fisher's exact test for categorical variables, the independent samplest test for normally distributed continuous variables, and the The Mann-Whitney U test when the distribution was skewed. A correlation was evaluated by the Spearman's rank correlation test. A p-value of 0.05 was considered statistically significant. We used a univariate analysis to quantify the association of variables with MPE. Variables found to be statistically significant in the univariate analysis ($p<0.250$) were used in a multivariate logistic regression model with the forward stepwise method to determine the independent associated factors of MPE. All statistical procedures were performed using the SPSS software version 14.0 (SPSS Inc., Chicago, IL).

RESULTS

A total of 114 COVID-19 patients with a mean age of 51.44±16.62 years and a female: male ratio of 0.4:1 were included in the study. Of the 114 COVID-19 patients included in the study, MPE was observed in 44, while it was not in 70. None of the patients had a history of any dermatological disorder. The demographic and clinical characteristics of the patients are shown in Table 1.

All patients with MPE had trunk and extremity involvement (Figure 1). Lesions were also present on the face and neck (Figure 2) in 12 patients (27.2%). Some patients reported mild pruritus. Ten patients received oral antihistamine therapy due to severe pruritus, while three were managed with short-term systemic corticosteroids. Maculopapular rash completely resolved within a mean duration of 2.8±0.5 days.

When the two groups were compared in terms of clinical features, fever, myalgia, dyspnea, anosmia, ageusia, rhinorrhea, and/or nasal congestion were found to be significantly higher in the MPE group (Figure 3). Although sore throat, diarrhea, and nausea/vomiting were more common in the MPE group, this difference was not statistically significant (Table 1).

As shown in Table 2, among the laboratory findings, the median values of Cr, ALP, GGT, LDH, vitamin D, ESR, procalcitonin, ferritin, fibrinogen, hemoglobin, red blood cell, monocyte, eosinophil and basophil counts were significantly higher in COVID-19 patients with MPE.

Table 1. Comparison of COVID-19 patients with and without maculopapular eruption according to demographic and clinical characteristics

	Patients with MPE n=44	Patients without MPE n=70	p-value
Sex, n (%)			
Female	12 (27.3)	20 (28.6)	0.881
Male	32 (72.7)	50 (71.4)	
Age (years), mean ± SD	59.7±18.2	46.2±13.2	<0.001
Smoking, n (%)	4 (9.1)	13 (18.6)	0.266
Comorbidity, n (%)			
Hypertension	3 (6.8)	2 (2.9)	0.372
Diabetes mellitus	3 (6.8)	2 (2.9)	0.372
Fever, n (%)	13 (29.5)	8 (11.4)	0.029
Myalgia, n (%)	13 (29.5)	8 (11.4)	0.029
Dyspnea, n (%)	14 (31.8)	4 (5.7)	<0.001
Sore throat, n (%)	9 (20.5)	8 (11.4)	0.295
Rhinorrhea and/or nasal congestion, (n %)	8 (18.2)	4 (5.7)	0.038
Diarrhea, n (%)	6 (13.6)	3 (4.3)	0.086
Nausea/vomiting, n (%)	5 (11.4)	3 (4.3)	0.257
Anosmia, n (%)	37 (84.1)	35 (50)	<0.001
Ageusia, n (%)	36 (81.8)	10 (14.3)	<0.001
Pulmonary involvement on CT, n (%)	42 (95.5)	70 (100)	0.147
≥50%	5 (11.9)	3 (4.3)	0.149

CT: Computed tomography, MPE: Maculopapular eruption, SD: Standart deviation, COVID-19: Coronavirus disease 2019

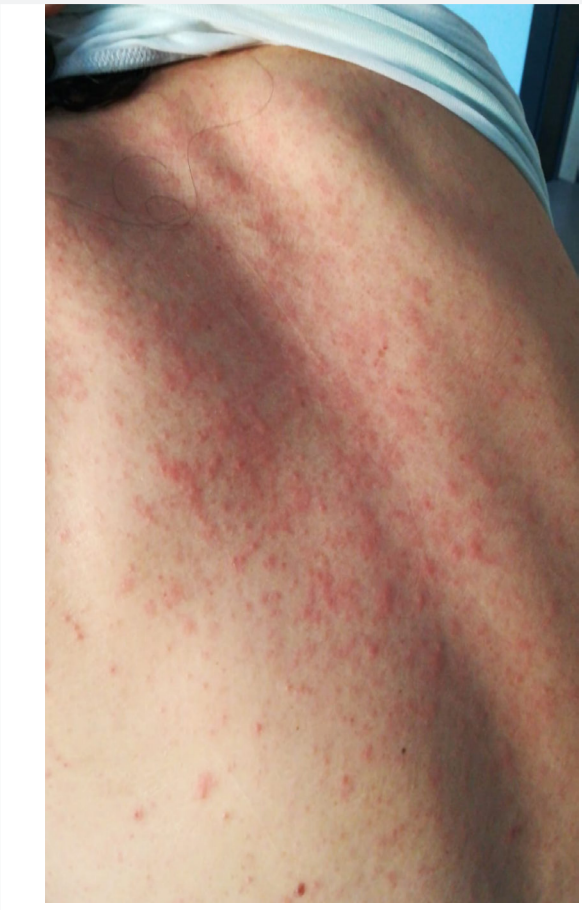

Figure 1. Maculopapular lesions on the trunk

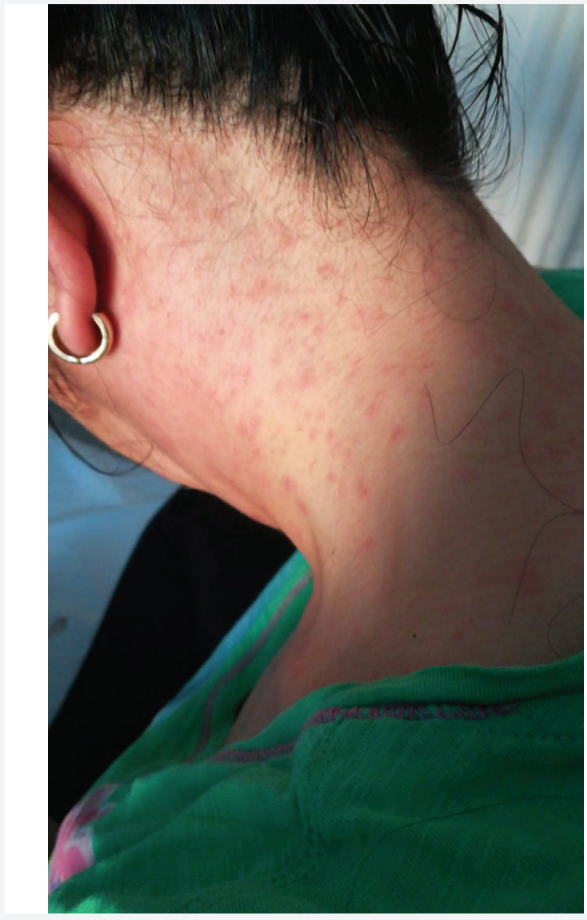

Figure 2. Maculopapular lesions on the neck

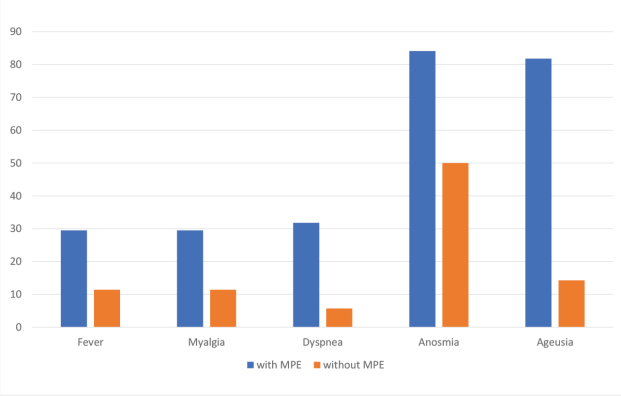

Figure 3. Clinical findings with statistically significant differences between COVID-19 patients with and without maculopapular eruption

COVID-19: Coronavirus disease 2019, MPE: Maculopapular eruption

Graphical results of the clinical findings found to be statistically significant in our study. It is not taken from any source and is the graph we created with statistical results

There was no significant difference between the two groups in any other parameters, including pulmonary involvement, smoking, and comorbidity.

In the multivariate logistic regression model, ALP was independently associated with MPE in COVID-19 patients (odds ratio: 1.099, 95% confidence interval: 1.056-1.144, p<0.001).

DISCUSSION

Dermatological involvements in COVID-19 patients can be examined in two groups from a pathophysiological perspective: (1) cytokine storm and inflammation that develop as an immune response to viral nucleotides, (2) vascular damage that develops as a result of vasculitis, vasculopathy, and thrombosis. MPE is in the first group, inflammation and cytokine storm are blamed for its pathogenesis[2-4].

The cytokine storm is thought to be the most important trigger of organ damage during COVID-19[3]. It develops owing to inflammatory reactions caused by activated T lymphocytes, monocytes-macrophages, and inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6),

Table 2. Comparison of COVID-19 patients with and without maculopapular eruption according to laboratory findings

	Patients with MPE n=44	Patients without MPE n=70	p-value
Complete blood count parameters			
WBC, (10^3/uL), median (range)	8.55 (3.10-17.50)	6.45 (3.10-17.50)	0.066
RBC, (10^6/uL), mean ± SD	4.07±0.58	3.83±0.68	0.049
HGB, (g/dL), mean ± SD	13.87±1.85	12.74±1.06	<0.001
PLT, (10^3/uL), median (range)	221.5 (134-461)	200 (134-200)	0.073
LYM, (10^3/uL), median (range)	1.32 (0.50-4.10)	1.50 (0.60-4.20)	0.091
MON, (10^3/uL), median (range)	1.20 (0.23-11.20)	1.03 (0.44-1.88)	0.031
EOS, (10^3/uL), median (range)	00 (0.25-2.10)	0.61 (0.36-1.03)	<0.001
BAS, (10^3/uL), median (range)	0.28 (0.00-0.90)	0.00 (0.00-0.66)	<0.001
Inflammation parameters			
ESR, (mm/hr), median (range)	34.50 (11.00-99.00)	22.50 (9.00-66.00)	0.001
CRP, (mg/L), median (range)	1.84 (0.41-1.84)	3.05 (0.10-9.46)	0.243
Procalcitonin, (ng/mL) median (range)	0.74 (0.05-40.00)	0.47 (0.10-1.55)	<0.001
Ferritin, (ng/mL), median (range)	405.0 (82.0-980.0)	102.50 (68.0-266.0)	<0.001
Coagulation parameters			
PT, (s), mean ± SD	0.92±0.33	0.95±0.29	0.677
Fibrinogen, (mg/L), mean ± SD	456.32±196.10	337.99±126.97	0.001
D-dimer, (g/L), median (range)	224.5 (28.00-2066.0)	226.0 (100.0-980.0)	0.269
Other biochemical parameters			
ALT, (U/L), median (range)	20.90 (5.40-123.20)	22.00 (6.30-78.00)	0.843
AST, (U/L), median (range)	25.00 (10.20-216.90)	23.60 (10.00-78.00)	0.163
GGT, (U/L), median (range)	33.00 (7.00-147.00)	23.00 (9.00-75.00)	0.025
LDH, (U/L), median (range)	137.0 (55.00-980.0)	111.85 (55.00-296.3)	<0.001
ALP, (U/L), median (range)	77.10 (29.00-200.00)	40.75 (22.80-77.00)	<0.001
Cr, (mg/dL), median (range)	0.62 (0.10-1.78)	0.33 (0.10-0.99)	<0.001
Uric acid, (mg/dL), mean ± SD	4.04±1.68	3.68±0.64	0.242
Albumin, (g/dL) mean ± SD	3.66±0.52	3.80±0.32	0.147
Ca, (mg/dL), mean ± SD	8.76±0.58	8.71±0.35	0.652
Mg, (mg/dL), mean ± SD	2.00±0.58	1.90±0.16	0.325
Vitamin D, (ng/mL), median (range)	33.00 (13.00-81.00)	27.00 (12.00-66.00)	0.003

ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, Ca: Calcium, Cr: Creatinine, CRP: C-reactive protein, ESR: Erythrocyte sedimentation rate, GGT: Gamma-glutamyl transferase, HGB: Hemoglobin, LDH: Lactate dehydrogenase, LYM: Lymphocyte, Mg: Magnesium, MON: Monocyte, MPE: Maculopapular eruption, PLT: Platelet, PT: Prothrombin time, RBC: Red blood cells, SD: Standart deviation, WBC: White blood cell, COVID-19: Coronavirus disease 2019, EOS: Eosinophil, BAS: Basophil

and interferon (IFN). It also plays a role in the pathogenesis of MPE[2-4]. In this context, the degree of inflammation and organ damage might be expected to be more severe in patients with MPE. Accordingly, in the current study, fever, myalgia-like inflammation symptoms, and inflammatory markers such as ESR, procalcitonin, and ferritin were significantly higher in COVID-19 patients who developed MPE. Moreover, Cr, ALP, GGT, and LDH, which indicate organ damage, were significantly higher in the MPE group.

SARS-CoV-2 must bind to the angiotensin-converting enzyme 2 (ACE2) receptor on the cell surface to enter the host cell and cause damage. Another factor in the development of MPE in COVID-19 patients is the direct damage caused by SARS-CoV-2 through ACE2 receptors on the surface of keratinocytes[5]. Cholangiocytes also contain a large number of ACE2 receptors on their surfaces[6,7]. Recent studies have shown that ACE2 was an IFN-stimulating gene, and the number of ACE2 receptors was increased through IFN and Toll-Like receptor-4 activation during inflammation[8,9]. Thus, the inflammation in the course of MPE might increase the number of ACE2 receptors. As a result, more cholangiocyte damage might occur in COVID-19 patients with MPE. This study has also detected higher levels of ALP and GGT in the MPE group, indicating cholangiocyte damage.

On the other hand, a recent study has shown that the SARS-CoV-2 spike protein could bind to the asialoglycoprotein receptor-1 found in primary human hepatocytes and hepatocyte-like cells in addition to the ACE2 receptor[10]. In other words, besides the ACE2 receptor, asialoglycoprotein receptor-1 has an additional effect on hepatocyte damage. In our study, there was no significant difference between the groups regarding the markers of primary hepatocyte damage, such as ALT and AST. In contrast, ALP and GGT levels, indicating cholangiocyte damage, were higher in the MPE group. Since the only entry route of SARS-CoV-2 into cholangiocyte cells is ACE2 receptors, cholangiocytes may be more affected than hepatocytes in patients with MPE. Furthermore, one of the most important results of our study was the independent association of ALP with the development of MPE in COVID-19 patients.

Apart from cholangiocytes, the ACE2 receptor is also found in large numbers on renal tubular cells, the tongue, olfactory epithelium, and buccal mucosa[6,7]. Higher Cr value and higher incidence of rhinorrhea and/or nasal congestion, anosmia, and ageusia in the MPE group might also be related to the increased number of ACE2 receptors in these anatomical regions. Another factor responsible for the development of anosmia and ageusia is TNF-α-mediated inflammation. TNF-α-related inflammation, which is also responsible for the development of MPE, might have contributed to the higher incidence of anosmia and ageusia in the MPE group[11-13]. On the other hand, these signs and symptoms were not reported in all COVID-19 patients. Their higher frequency in MPE patients might be related to individual and ethnic variabilities regarding ACE2 gene expression[14].

In the current study, among complete blood count parameters, monocyte, basophil, and eosinophil counts were found to be higher in the MPE group. Monocytes and macrophages are the mononuclear phagocyte system's primary cells that play a role in innate and adaptive immunity. Zhang et al.[15] reported that the number of monocytes in the peripheral blood of COVID-19 patients and the healthy population was similar. However, it has also been suggested that increased numbers of granulocyte-macrophage colony-stimulating factor+ monocytes and IL-6+ monocytes in the peripheral blood were responsible for the inflammatory cytokine storm in COVID-19 infection[16,17]. In this context, it is not surprising that the number of monocytes was higher in the MPE group, in which the cytokine storm was blamed for the pathogenesis.

Although there is no apparent effect of SARS-CoV-2 on eosinophils and basophils, a reduction in both cell groups is generally expected in COVID-19 patients. Both basophils and eosinophils can produce IL-4, an essential cytokine that stimulates the proliferation of activated T cells[18]. Thus, an increase in eosinophils and basophils might have contributed to the development of MPE in the setting of COVID-19 through T cell activation and cytokine storm. An increased number of basophils and eosinophils may be a cause and/or consequence of the development of MPE in COVID-19 patients. Although eosinophilia is an expected finding in drug-induced MPE[19], the rate of eosinophilia was also high in our COVID-19 patients with MPE, who had no history of recent medication initiation.

SARS-CoV-2, an RNA virus, mutates frequently and the infectiousness, virulence, effects on the immune system, mortality rate, and the presence of clinical findings such as anosmia and ageusia of newly emerging variants may differ. According to the WHO epidemiological update of December 11, 2021, five SARS-CoV-2 variants have been identified since the beginning of the pandemic: Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1), Delta (B.1.617.2), Omicron (B.1.1.529). The first of these variants, the Alpha (B.1.1.7) variant, was reported in late December 2020 in the United Kingdom[20].

Study Limitations

The main limitation of the study is that it did not include the long-term results of the patients due to its retrospective cross-sectional design. Moreover, the number of samples was relatively small due to its single-center design. The other limitation is the lack of COVID-19 mutation analysis. Since we could not perform mutation analysis in our study, we excluded patients diagnosed with COVID-19 after December 2020 in order not to evaluate patients with possible different mutations. However, the main strength of our study was the exclusion of suspicious cases with negative PCR tests and MPE following the onset of any medication.

CONCLUSION

ALP was independently associated with MPE in COVID-19 patients. In addition, the disease may progress more severely in COVID-19 patients with MPE due to increased inflammatory response. Several COVID-19 cases presenting with MPE as the first sign of infection were reported in the literature. It is essential to isolate these patients in the early period and to follow them closely in terms of possible severe disease courses.

Ethics

Ethics Committee Approval: Ethical approval was received from the Çanakkale Onsekiz Mart University Clinical Research Ethics Committee (decision no: 2022/15-05, date: 30.11.2022).

Informed Consent: This retrospective comparative study assessed COVID-19 patients with MPE followed up in our single tertiary center.

Footnotes

Authorship Contributions

Surgical and Medical Practices: Ö.K, S.A., S.I.M., S.O.K., Concept: Ö.K, S.A., S.I.M., Design: Ö.K, S.A., S.I.M., S.O.K., Data Collection or Processing: Ö.K, S.A., S.I.M., H.Y.C., S.O.K., Analysis or Interpretation: Ö.K, S.A., S.I.M., H.Y.C., S.O.K., Literature Search: Ö.K, S.O.K., Writing: Ö.K, S.A., S.I.M., H.Y.C., S.O.

Conflict of Interest: No conflict of interest was declared by the authors.

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