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IMPACT OF COVID-19 ON GRANULOMATOSIS WITH POLYANGIITIS: A RETROSPECTIVE ANALYSIS OF INCIDENCE AND CLINICAL CHARACTERISTICS

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Abstract

Aim: This study aimed to evaluate the impact of the coronavirus disease-2019 (COVID-19) pandemic on the incidence and clinical characteristics of granulomatosis with polyangiitis (GPA) in patients diagnosed before and after the onset of the pandemic.

Material and Methods: A retrospective analysis was conducted on 67 patients diagnosed with GPA between 2012 and 2023, categorized into pre-pandemic (n=35) and post-pandemic (n=32) cohorts. Data on sociodemographic, laboratory, and clinical characteristics were collected and statistically analysed.

Results: The incidence of GPA increased from approximately 0.58 to 1.07 cases per 100,000 person-years post-pandemic. No statistically significant differences were observed in most clinical parameters, although a notable rise in alkaline phosphatase levels was identified (p=0.016). The demographic analysis revealed a higher prevalence of male patients in the post-pandemic group (p=0.020). Despite the increased incidence, mortality rates and clinical features remained stable between the two periods.

Conclusion: The findings suggest a significant association between the COVID-19 pandemic and the increased incidence of GPA, potentially linked to immune dysregulation triggered by severe acute respiratory syndrome coronavirus 2 infection. While the clinical management of GPA has remained effective, the need for heightened awareness of autoimmune conditions in the context of COVID-19 is emphasized, warranting further investigation into the long-term implications of viral infections on autoimmune diseases.

Keywords: Autoimmune disease, COVID-19, granulomatosis with polyangiitis, incidence

INTRODUCTION

The outbreak of coronavirus disease-2019 (COVID-19) due to severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) has had serious consequences on a global scale, including in people with chronic autoimmune diseases. Given the increased morbidity and mortality rates during the pandemic, concerns have been raised about the exacerbation of autoimmune diseases and the emergence of new autoimmune phenomena. Research suggests that SARS-CoV-2 infection may lead to various autoimmune diseases by triggering autoimmune responses through mechanisms such as molecular mimicry, epitope spreading, and immune dysregulation (1-5).

Recent studies suggest a possible link between SARS-CoV-2 and the development of granulomatosis with polyangiitis (GPA), a vasculitis associated with antineutrophil cytoplasmic antibody (ANCA). GPA is characterized by necrotizing granulomatous

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inflammation affecting small- to medium-sized blood vessels and is often associated with respiratory symptoms such as cough and hemoptysis (6,7). It has been hypothesized that hyperactivation of the immune system during the process of infection with the SARS-CoV-2 virus, which can potentially result in elevated levels of autoantibodies, may act as a mechanism that may initiate the onset of GPA in individuals who are genetically predisposed to such an outcome (6,8,9).

A review of the literature revealed numerous case reports documenting the occurrence of GPA in patients infected or vaccinated with SARS-CoV-2. Furthermore, there is evidence that if a patient receiving SARS-CoV-2 treatment develops GPA, it may present challenges in the treatment and management of the patient (7,10). As evidenced by case reports of ANCA-associated vasculitis following vaccination to prevent the development of SARS-CoV-2, the mechanism that initiates vasculitis formation may be linked to the vaccination itself (11,12).

The exact mechanism by which SARS-CoV-2 contributes to GPA is not known. However, the pandemic has caused a notable increase in autoimmune diseases, highlighting the need for healthcare professionals to be vigilant about the potential for SARS-CoV-2 to induce or exacerbate autoimmune diseases.

In conclusion, there is a need for studies that examine the sociodemographic, laboratory, clinical, and outcome characteristics of autoimmune diseases during the post-pandemic period. As the world continues to experience the effects of the pandemic, understanding these dynamics will be critical for improving patient care and outcomes in individuals with autoimmune diseases.

The aim of this study was to assess the impact of the pandemic on patients with GPA by comparing the sociodemographic, laboratory, and clinical characteristics of patients in our GPA cohort before and after the onset of the SARS-CoV-2 pandemic.

MATERIALS AND METHODS

The present study retrospectively examined patients diagnosed with GPA in the rheumatology department between 2012 and 2023. The patients were grouped according to the timing of their diagnosis before or after 11 March 2020, the start date of the SARS-CoV-2 pandemic in Turkey. After reviewing the patient files and hospital information system, cases that met the 2022 Acr/Eular criteria were identified and included in the study cohort of patients with granulomatous polyangiitis.

The sociodemographic data, laboratory results, and clinical involvement characteristics used in this study were sourced from the hospital automation system and patient files. The data employed in the statistical analyses were the baseline values recorded at the time of GPA diagnosis in both groups. A total of 67 patients were included in the study, comprising 35 cases diagnosed with GPA prior to the onset of the SARS-CoV-2 pandemic and 32 cases diagnosed with GPA subsequent to the onset of the pandemic.

This study was approved by the Fırat University Non-Interventional Research Ethics Committee (approval no.: 2024/12-21, date: 11.09.2024) and was conducted in accordance with the tenets set forth in the Helsinki Declaration. The retrospective nature of the study, combined with its ethical oversight, provides a solid foundation for the findings, allowing for insights into the ramifications of the SARS-CoV-2 pandemic on GPA cases.

Statistical Analysis

The data underwent statistical analysis using the appropriate tests to compare the two groups. Continuous variables were analyzed using either Welch's t-test or Student's t-test, while Levene's test was employed to assess the equality of variances. Chi-square tests were employed for categorical data, thereby ensuring a robust statistical framework for the analysis of differences in clinical characteristics and outcomes between the two cohorts.

RESULTS

The institution where the study was conducted was not a healthcare facility where patients with confirmed or suspected SARS-CoV-2 infection could receive inpatient or outpatient treatment or vaccination during the pandemic period. As a result, it was not possible to gather data regarding vaccination and infection status in patients with GPA diagnosed during the post-COVID-19 period. Nevertheless, the official data indicate that the rate of at least one vaccination dose in the region where the study was conducted was 71.4%, and that approximately 20% of the country's population was infected with the SARS-CoV-2 virus. Furthermore, the study region has not been affected by natural disasters or migration, which could have resulted in changes to the sociodemographic structure during the post-pandemic period.

The analysis indicates that the incidence of GPA increased from approximately 0.58 cases per 100,000 person-years in the pre-pandemic period to approximately 1.07 cases per 100,000 person-years in the post-pandemic period.

A comparative analysis of the clinical parameters and demographic characteristics of patients with GPA before and after the beginning of the SARS-CoV-2 outbreak is presented in Table 1.

The analysis of clinical parameters in patients with GPA revealed no statistically significant differences in most parameters when comparing the pre-COVID-19 period (n=35) to the post-COVID-19 period (n=32). The mean age of patients in the pre-COVID-19 group was 53.2±13.8 years, whereas that in the post-COVID-19 group, it was 49.0±14.8 years (p=0.246).

Among the laboratory parameters, c-ANCA (Enzyme-Linked Immunosorbent Assay (ELISA) levels showed a mean of 68.3±40.4 in the pre-COVID-19 group compared to 52.5±43.4 in the post-COVID-19 group (p=0.129). p-ANCA (ELISA) levels increased from 7.8±26.1 to 18.4±36.8 [minimum-maximum (min.-max.): 3-100, both] (p=0.183). Furthermore, no notable

Table 1. Comparative analysis of clinical parameters in GPA patients before and after the onset of the SARS-CoV-2 pandemic

	Pre-COVID-19 period (n=35)	Post-COVID-19 period (n=32)	p-value
Age (years)	53.2±13.8	49.0±14.8	0.246[x]
C-ANCA (ELISA) (AU/mL)	68.3±40.4	52.5±43.4	0.129[x]
P-ANCA (ELISA) (AU/mL)	3-100[b]	3-100[b]	0.183[a +]
CRP (mg/L)	96.4±62.5	106.0±75.8	0.570[x]
ESR (mm/h)	79.3±30.6	75.5±33.9	0.633[x]
GFR (mL/dk/1.73 m^2)	55.8±35.4	53.1±34.1	0.751[x]
Urea (mg/dL)	83.4±64.5	89.6±80.3	0.729[x]
Creatine (mg/dL)	2.05±1.93	2.62±2.76	0.324[x]
Uric acid (mg/dL)	1.7-9.8[b]	2.4–14.4[b]	0.407[a +]
Uric acid/creatine ratio	4.24±2.68	3.62±1.97	0.296[x]
Total protein (g/dL)	6.50±0.80	6.48±0.77	0.949[x]
Albumin (g/dL)	3.47±0.66	3.60±0.62	0.415[x]
T protein/alb ratio	1.91±0.29	1.83±0.29	0.314[x]
AST (U/L)	6-111[b]	12-285[b]	0.077[a +]
ALT (U/L)	2-142[b]	7-665[b]	0.112[a +]
GGT (U/L)	2-325[b]	6-549[b]	0.084[a +]
ALP (U/L)	19-144[b]	26-281[b]	**0.016**[a +]
LDH (u/L)	251.6±115.5	270.3±156.2	0.577[x]
Total biluribin (mg/dL)	0.47±0.22	0.68±0.94	0.206[x]
Direct biluribin (mg/dL)	0.1-0.4[b]	0.1-4.1[b]	0.240[a +]
Hemoglobin (g/dL)	10.4±2.53	10.3±2.57	0.885[x]
Haemotocrit (%)	32.1±7.94	31.4±8.00	0.719[x]
MCV (fL)	92.0±63.7	82.8±4.84	0.421[x]
Platelet (10e3/µL)	354.8±168.0	382.6±162.2	0.495[x]
Mpv (fL)	8.41±1.21	8.68±1.15	0.346[x]
WBC (10e3/µL)	10.9±4.32	11.1±5.11	0.861[x]
Neu (10e3/µL)	8.44±3.69	8.73±4.78	0.776[x]
Lym (10e3/µL)	1.49±0.73	1.40±0.64	0.581[x]
Neu/Lym ratio	8.66±9.71	8.20±7.50	0.833[x]
Overall duration of disease (Weeks)	242.1±198.6	240.9±205.9	0.980[x]
Time to mortality post-disease onset (Weeks)	8-148[b]	3-432[b]	0.503[a +]

[a]Levene's test is significant (p<0.05), suggesting a violation of the assumption of equal variances, [b]Minimum-maximum value, [+]Welch's test p-value, [x]Student's t-test, p-value, c-Anca: Antineutrophil cytoplasmic autoantibody, cytoplasmic, p-Anca: Perinuclear anti-neutrophil cytoplasmic antibodies, CRP: C-reactive protein, ESR: erythrocyte sedimentation rate, GFR: Glomerular filtration rate, AST: Aspartate aminotransferase, ALT: Alanine aminotransferase, GGT: Gamma-glutamyl transferase, ALP: Alkaline phosphatase, MCV: Mean corpuscular volume, MPV: Mean platelet volume, WBC: White blood cells, Neu: Neutrophil, Lym: Lymphocyte

discrepancy was detected in terms of C-reactive protein levels, erythrocyte sedimentation rate, urea, creatinine, uric acid, uric acid/creatinine ratio, total protein, albumin, and protein/alb ratio.

Liver function tests indicated a significant elevation in alkaline phosphatase (ALP) levels from 78.4±29.5 to 110.5±66.3 (min.-max. 19-144, 26-281 respectively) (p=0.016). Other parameters, including complete blood count, showed no significant changes over the two periods.

The statistical analysis indicated that the overall duration of disease was comparable between the pre-COVID-19 group (242.1±198.6 weeks) and the post-COVID-19 group (240.9±205.9 weeks), with a p-value of 0.980, suggesting no statistically significant difference. In contrast, the time to mortality post-disease onset was notably longer in the post-COVID-19 group (94.6±147.3 weeks) (min.-max. 3-432 weeks) than in the pre-COVID-19 group (56.8±47.1 weeks) (min.-max. 8-148 weeks). However, this change was not statistically significant (p=0.503).

A comparative analysis of categorical demographic and laboratory parameters in GPA before and after the onset of the SARS-CoV-2 pandemic is presented in Table 2.

The demographic analysis indicated a significant difference in gender distribution, with a chi-square value of 5.43 (p=0.020), suggesting a higher prevalence of male patients in the post-COVID-19 group. No statistically significant difference was observed in the positivity rates of ANCA Immunofluorescence assay (IFA) (PR3 a/o MPO ANCA) between the two study periods (p=0.08). The analysis of ANCA (ELISA) status exhibited no relevant changes in the presence of c-ANCA and p-ANCA between the two periods (p=0.29, 0.27 respectively).

The spot urine protein:creatinine ratio analysis indicated no significant differences in the severity of proteinuria between the two periods (p=0.53).

A comparative analysis of the categorical clinical manifestations and outcome parameters in patients with GPA before and after the onset of the SARS-CoV-2 pandemic is presented in Table 3.

The clinical manifestations of GPA were evaluated, demonstrating no notable discrepancies in the occurrence of glomerulonephritis, pulmonary hemorrhage, non-cavitating pulmonary nodules, retro-orbital disease, episcleritis, nasal and paranasal disease, myositis, central nervous system, meningeal, cardiac, or mesenteric involvement from pre- to post-COVID-19 era.

However, the analysis of mortality rates indicated that 12 patients died in the pre-COVID-19 period compared with 8 in the post-COVID-19 period (p=0.407), suggesting no significant change in mortality rates. Moreover, the occurrence of life-threatening diseases and infections necessitating hospitalization does not exhibit a substantial change between the two intervals. (respectively p=0.987, p=0.853).

DISCUSSION

In this retrospective study of our cohort, we observed an increase in the incidence of GPA compared with the pre-pandemic period. Furthermore, we found that GPA was more common in

Table 2. Comparative analysis of demographic and laboratory parameters in in GPA patients before and after the onset of the SARS-CoV-2 pandemic

	COVID-19 period				
	Previously (n=35)	After (n=32)	χ^2	df	p-value
Male Female	13 (38%)	21 (62%)	5.43	1	0.020
	22 (66%)	11 (34%)			
Anca (IFA) + (PR3 a/o MPO) Anca (IFA) - (PR3 & MPO)	31 (88%)	4 (12%)	2.98	1	0.084
	23 (72%)	9 (28%)			
c-ANCA (ELISA) + c-ANCA (ELISA) -	28 (56%)	22 (44%)	1.12	1	0.29
	7 (41%)	10 (59%)			
p-ANCA (ELISA) + p-ANCA (ELISA) -	3 (30%)	7 (70%)	2.33	1	0.27
	32 (56%)	25 (44%)			
Normal&mild Spot urine protein/creatine ratio Modarate spot urine protein/creatine ratio Severe spot urine protein/creatine ratio	22 (56%)	17 (44%)	1.27	2	0.53
	5 (38%)	8 (62%)			
	8 (53%)	7 (47%)			

Anca (IFA); Antineutrophil cytoplasmic antibodies (Immunofluorescence assay), c-Anca; Antineutrophil cytoplasmic autoantibody, cytoplasmic, p-Anca; Perinuclear anti-neutrophil cytoplasmic antibodies, PR3; Proteinase 3, MPO; Myeloperoxidase, df; Degrees of freedom

Table 3. Comparative analysis of clinical manifestations and outcomes in GPA patients before and after the onset of the SARS-CoV-2 pandemic

	COVID-19 period				
	Previously (n=35)	After (n=37)	χ^2	df	p-value
Glomerulonephritis +	20 (50%)	20 (50%)	0.199	1	0.655
Glomerulonephritis -	15 (55%)	12 (45%)			
Pulmonary haemorrhage +	11 (55%)	9 (45%)	0.0871	1	0.768
Pulmonary haemorrhage -	24 (51%)	23 (49%)			
Meningeal involvement +	1 (50%)	1 (50%)	0.00414	1	0.949
Meningeal involvement -	34 (52%)	31 (48%)			
CNS involvement +	7 (46%)	8 (54%)	0.241	1	0.624
CNS involvement -	28 (54%)	24 (46%)			
Retro-orbital disease +	1 (50%)	1 (50%)	0.001	1	0.965
Retro-orbital disease -	34 (52%)	31 (48%)			
Cardiac involvement +	4 (57%)	3 (43%)	0.075	1	0.784
Cardiac involvement -	31 (52%)	29 (48%)			
Mesenteric involvement +	3 (50%)	3 (50%)	0.01	1	0.980
Mesenteric involvement -	32 (52%)	29 (48%)			
Nasal&paranasal disease +	16 (47%)	18 (53%)	0.742	1	0.389
Nasal&paranasal disease-	19 (57%)	14 (43%)			
Skin involvement +	8 (50%)	8 (50%)	0.04	1	0.83
Skin involvement -	27 (53%)	24 (47%)			
Myositis +	2 (100%)	0 (0.0%)			0.493[a]
Myositis -	33 (51%)	32 (49%)			
Non-cavitating pulmonary nodules +	23 (56%)	18 (44%)	0.631	1	0.427
Non-cavitating pulmonary nodules -	12 (46%)	14 (54%)			
Episcleritis +	2 (50%)	2 (50%)	0.008	1	0.926
Episcleritis -	33 (52%)	30 (48%)			
Life/organ threatening diseases +	24 (52%)	22 (48%)	2.48	1	0.987
Life/organ threatening diseases -	11 (52%)	10 (48%)			
Mortality +	12 (60%)	8 (40%)	0.688	1	0.407
Mortality -	23 (49%)	24 (51%)			
Infection requiring hospitalisation +	15 (54%)	13 (46%)	0.034	1	0.853
Infection requiring hospitalisation -	20 (51%)	19 (49%)			

[a]Fisher's exact test, p-value
CNS: Central nervous system, GPA: Granulomatosis with polyangiitis, SARS-CoV-2: Severe acute respiratory syndrome-coronavirus-2, df; Degrees of freedom

men during the post-pandemic period. Additionally, we did not observe a significant difference between the pre-pandemic and post-pandemic periods in terms of many clinical and laboratory parameters, including important parameters such as infection requiring hospitalization and mortality.

The elevated incidence observed in the present study may be attributable to an exaggerated and aberrant inflammatory response to SARS-CoV-2. It has been demonstrated that the SARS-CoV-2 virus can elevate the levels of inflammatory cytokines, including interleukin 6, 10, 17, 18, 22 and tumor necrosis

factor-alpha, in infected patients (13,14). In some cases, this exaggerated immune response manifests as a cytokine storm. This hypothesis is supported by several case reports that documented the development of GPA or the exacerbation of existing GPA in patients following a diagnosis of SARS-CoV-2 infection. This evidence suggests that the virus may act as a trigger for such autoimmune responses (6,7,15-17). The pandemic has also resulted in increased awareness and diagnosis of GPA, as healthcare systems have adapted to recognize and treat autoimmune conditions that are exacerbated by viral infections (18). Furthermore, the psychological distress and anxiety associated with the pandemic may exacerbate autoimmune conditions, underscoring the necessity for comprehensive care that addresses both physical and mental health (19,20).

Furthermore, it has been postulated that SARS-CoV-2 may precipitate vascular inflammation and vasculitis by directly affecting endothelial cells (21). The inflammatory response induced by SARS-CoV-2, which is typified by a cytokine storm, may additionally predispose individuals to autoimmune phenomena (15,22). The presence of antineutrophil cytoplasmic antibodies (ANCA) has been observed in some patients who have recovered from coronavirus SARS-CoV-2 infection, indicating that the virus may contribute to the dysregulation of the immune system (8,16).

It is possible that immunodysregulation caused by SARS-CoV-2 may increase the likelihood of GPA occurrence or exacerbate existing ones, as is the case in many rheumatic diseases (23). Additionally, several studies have indicated a rise in the prevalence of rheumatic disorders during the pandemic (24,25). For example, one study demonstrated an increase in the incidence of giant cell arteritis during the pandemic, indicating that the SARS-CoV-2 virus may have exacerbated the underlying pathogenetic mechanisms or triggered new cases (26).

In the context of our study, the fact that GPA was more common among male patients in the post-COVID-19 period than in the pre-COVID-19 period is another issue that needs to be discussed.

The male predominance in GPA cases according to COVID-19 may be due to natural differences in the immune response between the sexes and a stronger inflammatory response to viral infections in men. This observation is also consistent with the findings of the COVID-19 Global Rheumatology Alliance, which stated that male gender is an important risk factor for serious outcomes in rheumatic diseases during the pandemic (27,28).

The mean age of patients showed a slight decrease from the pre-COVID-19 period (53.2±13.8 years) to the post-COVID-19 period (49.0±14.8 years), although not statistically significant ($p=0.246$). The fact that patients with GPA were diagnosed at a younger age may be due to the fact that GPA has similar clinical features to SARS-CoV-2 and the effect of the pandemic on disease awareness (29).

The present study revealed no statistically significant difference in c-ANCA and p-ANCA (ELISA) levels (p-values of 0.129 and 0.183, respectively. This finding is consistent with the results of previous studies indicating that ANCA (ELISA) levels remain relatively stable in response to external stressors such as pandemics (30,31).

In this study, we observed that ALP values increased in patients with GPA in the post-COVID-19 period. This may be attributed to the higher male sex ratio of GPA patients in the post-COVID period. ALP levels are generally higher in men than in women for various physiological and hormonal reasons (32).

The lack of notable alterations in the majority of laboratory parameters indicates that the overall inflammatory profile remained unaltered, contrary to the hypothesis proposed in studies of a different nature (33).

Despite the observed increase in cases of GPA, the clinical features and outcomes have remained relatively stable. In the period following the pandemic, the clinical presentation pattern of GPA remained unchanged, with respiratory tract involvement and renal involvement being the most common (16,34). The prevalence of hospitalization among patients with GPA has remained consistent, indicating that the characteristics of the disease and the efficacy of established protocols for the management of severe cases have not undergone any significant alterations (35,36). The present study did not reveal any statistically significant increase in mortality rates among patients with GPA during the post-pandemic period. This indicates that although the incidence of COVID-19 is increasing, its overall management remains efficacious (37,38).

Moreover, the impact of the SARS-CoV-2 pandemic on chronic systemic autoimmune disorders has been subjected to rigorous scrutiny in numerous scientific studies. For example, individuals with autoimmune rheumatic disorders who contracted the virus showed similar hospitalization and mortality rates to those without autoimmune disease, suggesting that underlying autoimmunity may not markedly worsen the prognosis of SARS-CoV-2 infection (35,39). This observation is consistent with the findings of previous studies that indicated no significant differences in the clinical features or outcomes of patients with systemic autoimmune diseases during the pandemic (35,36). The consistent application of management strategies and the use of immunosuppressive therapies, such as rituximab, likely contributed to the maintenance of stable outcomes for patients with GPA despite the increased incidence (34,40). Moreover, the healthcare system's response to the pandemic, including

the prioritization of patients with severe COVID-19, may have unintentionally sustained the standard of care for GPA patients, ensuring that they continued to receive appropriate treatment despite the overwhelming impact of the pandemic. Furthermore, the prevalence of comorbidities in patients with GPA, which could potentially complicate their clinical course, has remained relatively unchanged during the pandemic, contributing to the observed stability in mortality rates.

Study Limitations

This study is limited by several factors, including the inherent biases associated with retrospective data collection and the relatively small sample size. Furthermore, the institution where the study was conducted was not a designated health center for the follow-up, treatment, and vaccination of patients with the virus. This was due to decisions taken by the relevant authorities, which meant that data on SARS-CoV-2 infection status and vaccination levels against it were not included.

CONCLUSION

In conclusion, the incidence of granulomatous polyangiitis increased following the onset of the SARS-CoV-2 pandemic. Despite the observed increase in the incidence of GPA, the clinical features, hospitalization, and mortality rates have remained stable. This stability may reflect the effectiveness of current treatment protocols and the success of health systems in managing chronic conditions in the context of a global health crisis.

Ethics

Ethics Committee Approval: This study was approved by the Fırat University Non- Interventional Research Ethics Committee (approval no.: 2024/12-21, date: 11.09.2024) and was conducted in accordance with the tenets set forth in the Helsinki Declaration.

Informed Consent: Retrospective study.

Footnotes

Authorship Contributions

Surgical and Medical Practices: B.Ö., Concept: B.Ö., G.Y., A.K., Design: B.Ö., G.Y., A.K., Data Collection or Processing: B.Ö., G.Y., İ.G., A.D.K., Y.D., A.K., Analysis or Interpretation: B.Ö., A.K., Literature Search: B.Ö., İ.G., A.D.K., Y.D., Writing: B.Ö.

Conflict of Interest: The authors have no conflicts of interest to declare.

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