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Effects of COVID-19 on axial spondyloarthritis disease flare

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ABSTRACT

Aims: Rheumatological disease flares may occur after many infections. However, our knowledge of the post-Coronavirus disease-2019 (COVID-19) axial spondyloarthritis (SpA) flares and related factors is limited.

Methods: We retrospectively assessed the axial SpA patients who had COVID-19. Demographic and clinical data were collected from the medical records. The Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was applied via telephone for pre- and post-COVID-19 SpA symptoms. An increase of ≥2 points in the BASDAI score or any new extra-articular manifestations were defined as SpA flares and SpA patients were grouped as flares and no-flare. Factors predicting SpA flare were also analyzed.

Results: A total of 48 axial SpA patients were included in the study [age, mean±standard deviation (SD): 42.3±8.6 years; male: 65%]. Post-COVID-19 SpA flare was identified in 19 patients (40%), and new extra-articular manifestations were recorded in 6 patients (13%). Although the diagnosis of inflammatory bowel disease was more common in the flare group, the difference was not significant compared with that of the no-flare group. Other features of SpA and COVID-19 disease severity were similar between the flare and no-flare groups. In the flare group, the frequency of back pain (84% vs. 62%, p=0.091) and diarrhea (53% vs. 28%, p=0.080), and headache (84% vs. 52%, p=0.021) were higher than the no-flare group. No risk factor for a post-COVID-19 SpA flare could be identified.

Conclusions: Post-COVID-19 flare was common in the axial SpA, and even new extra-articular manifestations could be reported. Although some clinical manifestations of COVID-19 were more common in patients with a flare, any predictive factor could not be identified among the study variables.

Introduction

The coronavirus disease-2019 (COVID-19) outbreak has become a major global health problem since December 2019. COVID-19 has heterogeneous clinical features ranging from an asymptomatic course to multi-organ failure. It is also a major cause of morbidity and mortality in some patients. In this context, patients with chronic diseases are more susceptible to these effects. The cascade of inflammatory mediators in COVID-19 may lead to many systemic symptoms (1,2). Although direct involvement of the skeletal muscles by viral agents has not been shown, approximately 15% of the cases could have arthralgia and myalgia at several sites (3).

Spondyloarthritis (SpA) refers to a group of chronic inflammatory arthritis, which can be further classified according to the distribution of joint involvement as predominantly axial (SpA) or peripheral SpA. Axial forms of SpA, which consist of ankylosing spondylitis and non-radiographic axial SpA are the most frequent types and usually present with chronic lower back pain, peripheral arthritis, enthesitis, dactylitis, or in association with extra-articular manifestations include psoriasis, uveitis, and inflammatory bowel disease (4,5). Non-steroidal anti-inflammatory drugs (NSAID) are frequently used in axial SpA patients along with other immunosuppressive and biological agents (6). Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), often used in daily practice, is a useful clinical scale

for both disease activation and flare determination of SpA patients (5,6).

Viral infections may cause arthritis, but the spectrum of these musculoskeletal symptoms is wide, ranging from arthralgia to peripheral chronic arthritis. Additionally, viral infections have also been linked to SpA-like disease (7). Furthermore, chronic inflammatory arthritis can be triggered by the Severe acute respiratory syndrome-Coronavirus-2 (SARS-CoV-2) infection, thus indicating that viral antigens can trigger systemic autoimmunity (8,9). Although there are some studies investigating the course of COVID-19 in various rheumatologic disorders, knowledge about the disease activation is scarce. Among the reasons leading to disease activity in these studies are disruptions in health services and drug use caused by the pandemic, and patients' delayed medical treatments due to fear of COVID-19 (10-12). So little is known about the post-COVID-19 disease activity of axial SpA patients. In this study, we evaluated the disease activity in patients with axial SpA following a COVID-19 diagnosis.

Methods

We conducted this retrospective, single-center, cross-sectional study at the Ankara City Hospital Rheumatology Clinic. Between 20 January 2021 and 10 January 2022, patients with a record of SARS-CoV-2 polymerized chain reaction (PCR) test results on nasopharyngeal swabs between 11 March 2021 and 01 January 2022 were screened using the Public Health Management System. All cases with a PCR test were registered in the database during the pandemic in the country. Among the SpA patients who were followed up, those who had a COVID-19 history were included in the study. Patients with a change for treating SpA in the last 6 months, coexisting rheumatic diseases, incomplete clinical data, patients older than 18 years, and pregnant were excluded from the study. Ethical approval for this study was obtained from the Ankara City Hospital Ethics Committee (approval number: E1-21-2154, date: 15.12.2021). The study protocol conforms to the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. The Turkish Ministry of Health, General Directorate of Health Services, approved the study protocol (2021-11-26T16_36_49).

A total of 361 axial spondyloarthropathy patients with COVID-19 were initially identified. The number of excluded subjects was 224 due to the following reasons; changes in the SpA-specific therapy in the last 6 months (n=130), coexisting rheumatic diseases (n=45), incomplete data (n=37), age than 18 years (n=6) and pregnancy (n=6).

Upon verbal consent, patients were interviewed via telephone for the post-COVID-19 symptoms, pre- and post-COVID-19 SpA treatment, and SpA symptoms. The demographics, disease characteristics, comorbidities, and medical therapies were confirmed through electronic medical records. Multimorbidity was defined as the presence of at least 2 or more comorbidities (13). The BASDAI was used in the clinical evaluation of SpA patients, which consists of 6 questions (14). The patient responds to the questions by considering events during the past week and scores the questions between 0 and 10, with 0 corresponding to "absent" and 10 corresponding to "very severe" (14). The BASDAI score is calculated by summing the average of the scores obtained from the fifth and sixth questions and the scores obtained from the first four questions and dividing the latter score by five. The validity and reliability of the Turkish version of the scale were previously reported (15). BASDAI was fulfilled for both pre-COVID and post-COVID SpA symptoms considering the situation two weeks before and after the infection. ≥2 points increase in the overall BASDAI score after COVID-19 was considered a disease flare (16). Additionally, the development of extra-articular manifestations was defined as a post-COVID flare. Axial SpA patients with and without post-COVID SpA flares were grouped as the "Flare group" and "No-flare group". All data were collected using a standardized case-report form by the same physician (BA).

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY). Descriptive data are presented as means with standard deviation (SD) and median with interquartile range (IQR). The normality of the distribution was tested by visual (histogram and probability graphs) and analytical (Kolmogorov-Smirnov and Shapiro-Wilk) tests. The chi-square test and Fisher's Exact test were used to compare the categorical variables between the groups. Where appropriate, Student's t-test and Mann-Whitney U test were used to compare the scale variables. Multivariable logistic regression analysis was performed to identify the factors independently associated with a post-COVID SpA flare. Hosmer-Lemeshow goodness of fit statistics was used to assess model fit. All tests of significance were two-sided and for statistical significance, a total type-1 error level of 5% was used.

Results

A total of 48 axial SpA patients were included in the study (age, mean±SD: 42.3±8.6 years, male: 65%). Demographic characteristics, comorbidities, and medical treatments for axial SpA are shown in Table 1. The percentage of patients with only non-steroidal anti-inflammatory drug treatment was 27% (n=13). Immunosuppressive treatment [sulfasalazine 29% (n=14), biological agents 38% (n=18), and sulfasalazine + biological agent 6% (n=3)] was identified in 73% (n=35) of the subjects.

During the post-COVID period, 29% (n=14) of the patients interrupted and/or discontinued their treatment, and 46% (n=22) had to increase their daily NSAID dosage. The distribution of the treatment agents in patients who interrupted and/or discontinued

their treatment was as follows: 13% (n=8) NSAID alone, 6% (n=3) sulfasalazine, 6% (n=3) biological agent, and 4% (n=2) sulfasalazine + biological agent. COVID-19 pneumonia was recorded by 10% (n=5), while 8% (n=8) of the sample was hospitalized and 6% (n=3) required oxygen support (Table 1). No patient was transferred to intensive care unit or died. The median±SD length of hospital stay was 6.0±0.7 days.

Nineteen (40%) of the patients had a flare of SpA symptoms in the post-COVID period. The pre-COVID median (IQR) BASDAI score was 4.7 (7.5), while the post-COVID score was 6.2 (p<0.001) (8). The comparison of the pre-COVID and post-COVID median scores of each question in the BASDAI between no-flare and flare groups is shown in Figure 1. There was no difference in terms of age, gender, disease duration, extra-articular involvement, peripheral arthritis, comorbidities, smoking, and SpA or COVID-19-specific medical treatment between patients with and without disease flare (Table 1). COVID-19 severity was also similar between the groups. When COVID-19 symptoms were compared, although back pain (84% vs 62%, p=0.091) and diarrhea (53% vs. 28%, p=0.080) were more common in the flare group, only headache was statistically higher in the flare group than the no-flare group. All the other COVID-19 symptoms between no-flare and flare groups were similar (Figure 2). In the post-COVID period, new extra-articular manifestations were observed in a total of 6 (13%) SpA patients including uveitis in 3, inflammatory bowel disease in

Table 1. Demographic and clinical characteristics, and medical treatment history of spondyloarthritis patients with and without disease flare

	Overall, n=48	No-flare group, n=29	Flare group, n=19	p
Age, years, mean±SD	42.3±8.6	41.2±9.5	43.8±6.7	0.297
Male, n (%)	31 (65)	21 (72)	10 (53)	0.161
Disease duration, years, median (IQR)	10.3 (9.0)	10.2 (9.7)	9.8 (8.5)	0.690
Smoking, n (%)	15 (31)	11 (38)	4 (21)	0.341
Psoriasis, n (%)	2 (4)	1 (3)	1 (5)	1
Uveitis, n (%)	9 (19)	6 (21)	3 (16)	0.726
Inflammatory bowel disease, n (%)	5 (10)	1 (3)	4 (21)	0.072
Peripheral arthritis, n (%)	17 (35)	10 (35)	7 (37)	0.854
Comorbidity, n (%)	29 (60)	16 (55)	13 (68)	0.359
Multimorbidity, n (%)	17 (35)	12 (41)	5 (26)	0.286
Hypertension, n (%)	7 (15)	4 (14)	3 (16)	0.580
Diabetes mellitus, n (%)	6 (13)	4 (14)	2 (11)	1
Obesity, n (%)	13 (27)	9 (31)	3 (21)	0.522
Hyperlipidemia, n (%)	3 (6)	2 (7)	1 (5)	0.657
Coronary artery disease, n (%)	5 (10)	4 (14)	1 (5)	0.635
Chronic obstructive pulmonary disease, n (%)	6 (13)	6 (21)	0	0.068
Spondyloarthritis specific treatments				
Biological agent, n (%)	21 (44)	12 (41)	9 (47)	0.683
NSAIDs, n (%)	23 (48)	15 (52)	8 (42)	0.514
Sulfasalazine, n (%)	15 (31)	9 (31)	6 (32)	0.968
Corticosteroid, n (%)	3 (6)	2 (7)	1 (5)	0.208
COVID-19 specific treatments				
Hydroxychloroquine, n (%)	11 (23)	7 (24)	4 (21)	0.708
Favipiravir, n (%)	36 (75)	21 (72)	15 (79)	0.609
COVID-19 severity				
Pneumonia, n (%)	5 (10)	3 (10)	2 (11)	0.376
Hospitalization, n (%)	4 (8)	1 (3)	3 (17)	0.343
Oxygen support, n (%)	3 (6)	1 (3)	2 (11)	0.254
Patients post-COVID features				
Post-COVID treatment continuation, n (%)	34 (71)	20 (69)	14 (74)	0.797
Post-COVID increased NSAID need, n (%)	22 (46)	9 (31)	13 (68)	**0.011**

SD: Standard deviation, IQR: Interquartile range, NSAID: Non-steroidal anti-inflammatory drugs, COVID-19: Coronavirus disease-2019

2, and psoriasis in 1. Although post-COVID AxSpA treatment continuation was similar between the two groups, post-COVID NSAID need was higher in the flare group than in the no-flare group (p=0.011).

In logistic regression analysis, male gender, presence of multimorbidity and history of inflammatory bowel disease, and COVID-19 symptoms such as fever, joint pain, back pain, and diarrhea were not independently associated with axial SpA flare (Table 2).

Discussion

In this study, 40% of patients with axial SpA had SpA flare in the post-COVID period, and 13% of the patients had newly emerged extra-articular manifestations. Although inflammatory bowel disease was more common in the flare group, the difference did not reach statistical significance. Other SpA features and COVID-19 disease severity were similar between the flame and no-flare groups. In comparison with the no-flare group, the frequency of the back headache, pain, and diarrhea was higher in the flare group; but, only the headache variable showed a statistically significant difference. Logistic regression analysis did not show any independent predictor of a post-COVID SpA flare.

In a study, which evaluated treatment adherence of 304 SpA patients during the COVID-19 pandemic, disease activity was observed in about 40% of patients (11). Except for the non-adherence to treatment, it was linked to the psychological effects of the COVID-19 pandemic and the disruption of daily physical activity (11). In another study that evaluated 287 SpA patients, it was observed that there was no significant increase in disease activity during the COVID-19 pandemic (10). The above-mentioned studies used a different methodology from our study, but viral agents may trigger SpA group diseases or cause flares (17,18). To the best of our knowledge, there is only one study in the literature that has evaluated SpA disease activity after COVID-19 (7). This study included 18 patients with psoriatic arthritis (PsA) and COVID-19 was associated with the PsA flares (7). Sporadic reports of cases with post-COVID SpA have commonly concluded that axial SpA clinical findings may be exacerbated, mostly in the form of reactive arthritis (8,19-21). Our study confirms the knowledge in the literature, as 40%

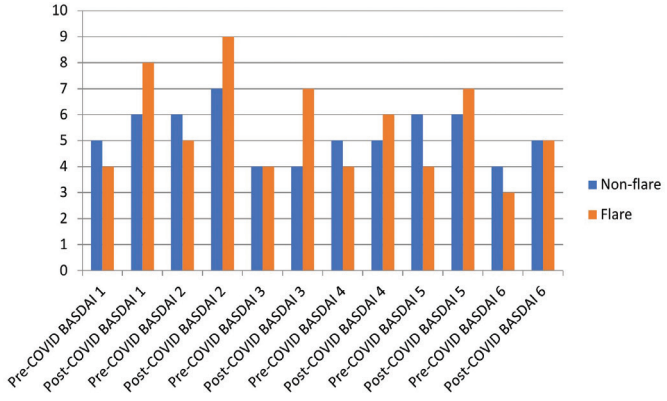

Figure 1. The comparison of the pre-COVID-19 and post-COVID-19 median scores (minimum-maximum: 0-10) of each BASDAI question between non-flare and flare groups

COVID-19: Coronavirus disease-2019, BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

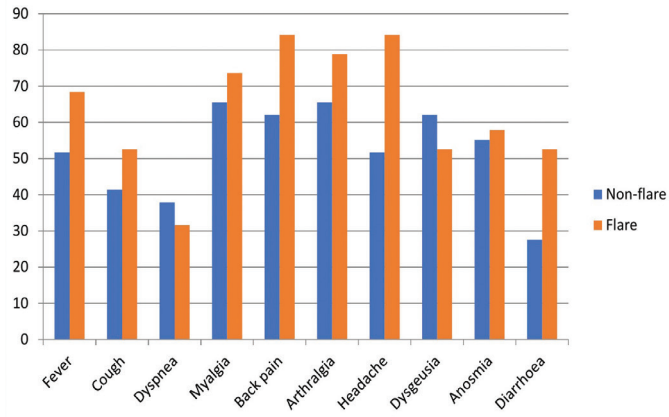

Figure 2. The comparison of all COVID-19 symptoms percentages between "non-flare" and "flare groups"

COVID-19: Coronavirus disease-2019

Table 2. Results of logistic regression analysis (outcome variable: spondyloarthritis flare)

	Univariate analysis		
Variables	**OR**	**95% CI**	**p**
Male gender	0.306	0.073-1.274	0.104
Multimorbidity	0.400	0.089-1.787	0.230
Inflammatory bowel disease	5.531	0.480-63.774	0.170
Fever	1.247	0.273-5.686	0.776
Arthralgia	0.575	0.049-6.794	0.660
Back pain	2.690	0.287-25.238	0.386
Diarrhea	2.405	0.486-11.912	0.282

OR: Odds ratio, CI: Confidence interval

of axial SpA patients had SpA flare after COVID-19. Moreover, age, extra-articular findings, presence of peripheral arthritis, and the medical treatment options used did not differ between the patients with and without a flare history.

COVID-19 may trigger several autoimmune pathways. Beyond the disease flares, patients with autoimmune rheumatic disease may also develop novel autoimmune characteristics such as psoriasis, vasculitis, and autoimmune colitis (22-24). Consistent with this, we found in our study that 13% of our patients had newly-emerging extra-articular SpA symptoms in the post-COVID period. Thus, it can be concluded that COVID-19 may cause new extra-articular manifestations in patients with axial SpA other than a classical disease flare.

Predisposing factors in the development of any joint involvement due to COVID-19 are still unknown. Prolonged exposure to the virus or more severe disease may lead to the spread of the virus to the respiratory and gastrointestinal tract, triggering autoimmunity (25). In the current sample of patients, headache, back pain, and diarrhea were more frequent in the SpA flare group. Apart from inflammatory load due to both axial SpA and COVID-19, upper respiratory tract obstruction due to COVID-19 and psychological factors could play a major role in the development of headache. Nevertheless, the mechanism of increased headache complaints in SpA patients with flare needs to be further studied.

Many reasons, such as treatment non-compliance, viral infections, physiological factors, and psychological stress, may cause flares in SpA patients (7,17,18). In logistic regression analysis, some conditions that may be associated with a post-COVID SpA flare were evaluated, but we could not find any predictor factor. The small number of patients in our study may be a reason why we could not find conditions related to disease flare in previous studies. Therefore, studies involving a larger number of patients could help us obtain clearer results in this regard.

Study Limitations

There are limitations to our study. Firstly, this was a retrospective study and the number of evaluable patients was low due to the inclusion criteria of only the patients with stable medical treatment in the last 6 months. We did not have stress, depression, or anxiety measures in this study, suggesting the presence of unmeasured confounding. Although the BASDAI score is useful for identifying the disease activations or flare, it is a patient-reported measure of disease activity and is mostly subjective. Another limitation is that NSAID use could not be defined and categorized objectively. The BASDAI questionnaire was completed via phone calls, which may have caused over or underestimation of the scores since physical examination data and the level of acute phase reactants were lacking. Lastly, some COVID-19 symptoms could be mixed with some questions in BASDAI. In order to better distinguish post-COVID SpA flare from the COVID-19 clinical findings, we carried out a BASDAI questionnaire considering 2 weeks previously and later. In the original BASDAI questionnaire, each question evaluates the previous week, so this condition precludes the generalizability of our results as exact SpA disease flares.

Conclusion

In conclusion, post-COVID flare is common in the axial SpA, and even new extra-articular manifestations may be observed. COVID-19 may induce disease flares in axial SpA patients, regardless of the ongoing rheumatological treatment. Diarrhea, back pain, and headache during COVID-19 may be the symptoms suggestive of a post-COVID flare in axial SpA patients.

Ethics

Ethics Committee Approval: This study was approved by the Ankara City Hospital Ethics Committee (protocol number: E1-21-2154, date: 15.12.2021). The Turkish Ministry of Health, General Directorate of Health Services, approved the study protocol (2021-11-26T16_36_49).

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship statement

Concept: B.A., O.K., A.E., Design: B.A., S.C.G., İ.D., Data Collection, or Processing: B.A., E.A., B.Ö., Ö.K., Analysis, or Interpretation: B.A., E.K.E., Literature Search: B.A., E.A., B.Ö., Ö.K., E.K.E., S.C.G., İ.D., O.K., Writing: B.A., A.E.

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