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Serum high-sensitivity C-reactive protein, tumor necrosis factor-α, interleukin (IL)-1β, IL-17A and IL-23 levels in patients with hidradenitis suppurativa

Gonca Saraç Öztürk [a,*], Tülin Ergun [a], İrem Peker Eyüboğlu [b], Mustafa Akkiprik [b]

[a] Department of Dermatology, Marmara University School of Medicine, Istanbul, Turkey
[b] Department of Medical Biology, Marmara University School of Medicine, Istanbul, Turkey

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ABSTRACT

Background: Hidradenitis suppurativa (HS) is a chronic, recurrent inflammatory skin disease that leads to scar formation. The immune pathogenesis of HS is not fully understood and inhibitors of tumor necrosis factor (TNF)-α, interleukin (IL)-17, IL-1, IL-23 can be used for treating HS. Identification of serum biomarkers may help understanding individual differences in HS pathogenesis, evaluating disease severity and developing more effective treatment methods.

Objectives: To assess the serum levels of proinflammatory cytokines TNF-α, IL-1β, IL-17A, IL-23 and high-sensitivity C-reactive protein (hs-CRP) in patients with HS and to evaluate the impact of treatment on cytokine levels.

Methods: Serum proinflammatory cytokine and hs-CRP levels were measured using enzyme-linked immunosorbent assay kits in 24 healthy controls and in 26 HS patients at baseline and after a 3-month treatment. Patients were treated with clindamycin, adalimumab, dapsone, doxycycline and acitretin, based on HS condition and laboratory results. Control, pre-treatment and post-treatment values were compared.

Results: HS patients had significantly higher hs-CRP levels than controls which decreased following treatment ($p = 0{,}010$, $p = 0{,}007$). No significant difference was found in serum levels of TNF-α, IL-1β, IL-17A, IL-23 compared to controls and post-treatment levels.

Conclusions: There is insufficient data to suggest TNF-α, IL-1β, IL-17A and IL-23 as serum biomarkers in HS. hs-CRP can be used as an indicator of treatment response and systemic inflammation.

1. Introduction

Hidradenitis suppurativa (HS) is a chronic inflammatory skin disease characterized by nodules, abscesses, sinus tracts and scar formation most frequently affecting inguinofemoral, axillary and anogenital regions [1]. HS has a significant negative effect on patient's quality of life due to recurrent purulent drainage, chronic pain, malodour and disfiguring scars [2]. The pathogenesis of HS is complicated and has multifactorial processes, with immune dysfunction having a pivotal role. While the primary event is generally thought to be follicular occlusion, perifollicular inflammation has recently been suggested as a companion and the main driver in the pathogenesis. [3]. Immune system cells and keratinocyte-derived cytokines have been demonstrated in the skin, serum and exudate of HS patients, but their roles in disease pathogenesis are not fully explained. Tumor necrosis factor (TNF)-α, interferon-γ, interleukin (IL)-1 pathway, IL-17/IL-23 axis, IL-6 and IL-10 are known to be highly expressed in HS. Cytokines are reported to contribute to follicular occlusion and cyst formation and are responsible for follicular rupture, tunnel formation, and systemic inflammation [3,4]. Chronic inflammation having systemic effects is thought to be related to increased prevalence of comorbidities such as metabolic syndrome, arthritis or inflammatory bowel disease (IBD) [5–8].

Current treatments of HS still do not provide adequate control of the disease. Although biologic therapies for suppressing the abnormal inflammatory activation is promising, adalimumab, currently the only approved biologic for the treatment of HS, does not have a dramatic efficacy as in psoriasis. In spite of promising results with tumor necrosis factor (TNF), IL-17, IL-23 and IL-1 inhibitors, cytokines/chemokines

* Corresponding author at: İstanbul Şile Devlet Hastanesi, Kumbaba Mahallesi, Uygur Sokak, No:267 Şile, İstanbul, Turkey.
E-mail address: goncasarac@yahoo.com (G. Saraç Öztürk).

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whose inhibition will provide the most sufficient effect in alleviating inflammation in HS are not yet known. Among several gaps in knowledge about HS, reliable and easily measurable serum biomarkers to determine disease severity and treatment response and also each individual's major inflammatory pathway which may allow optimal use of biologics, are important ones.

This study aims to evaluate TNF-α, IL-1β, IL-17A and IL-23 serum levels for identifying the master cytokine in the pathogenesis of HS and also to investigate the impact of treatment on cytokines levels. In addition, high-sensitivity (hs)-C-reactive protein (CRP) levels and its change with treatment was analyzed.

2. Materials and methods

2.1. Participants

The study population included 26 HS patients and 24 healthy control volunteers aged between 18 and 65 years. HS was diagnosed by a dermatologist according to the modified Dessau criteria. [1]. Participants who received a systemic anti-inflammatory therapy within four weeks prior to recruitment and with any other chronic inflammatory or autoimmune disease were excluded.

This study was approved by the Ethics Committee of the Marmara University School of Medicine (Protocol number: 09.2017.322) and performed according to the Declaration of Helsinki. A written informed consent obtained from all participants prior to enrolment.

2.2. Data and sample collection

Sociodemographic characteristics, medical histories and family histories of HS patients were recorded. HS severity was assessed with the modified Hidradenitis Suppurativa Score (mHSS) and HS-Physician global assessment (HS-PGA).

Serum samples were taken from all participants at the first visit and after three months of treatment from HS patients. Venous blood of 5 mL was collected in vacuum tubes under sterile conditions. The serum was separated by centrifugation, aliquoted and stored at −80 °C until analysis.

HS patients treated according to the guideline, based on their physical examination and laboratory test results. Topical 15% resorcinol solution and topical 1% clindamycin lotion were prescribed to all. Of the 26 patients, 14 received oral clindamycin 300 mg b.i.d., 8 adalimumab 40 mg weekly, 2 dapsone 100 mg/day, 1 doxycycline 100 mg b.i.d. and 1 acitretin 25 mg/day.

2.3. Measurement of cytokine and hs-CRP levels

TNF-α, IL-1β, IL-17A, IL-23 and hs-CRP levels were quantified from serum samples via commercially available enzyme-linked immunosorbent assay kits (Cat# BMS223/4, BMS224/2, BMS2017, BMS2023/3 eBioscience, San Diego, CA, USA and EIA-3954 DRG International Inc., USA respectively) according to the manufacturer instructions. IL-23 and hs-CRP were measured in all 76 serum samples, whereas TNF-α, IL-1β and IL-17A were detected in 44 (57.9%), 33 (43.4%) and 44 (57.9%) samples, respectively. Non-detectable values were left blank in statistical analyses.

2.4. Statistical analysis

Statistical analysis was performed using SPSS Statistics 23.0 (IBM Corp., Armonk, NY, USA). The normality of distribution of variables were assessed using Shapiro-Wilk test. Categorical variables are shown as frequency and percentage. Numerical variables are presented as mean and standard deviation for normally distributed variables and median and inter-quartile range (IQR) for non-normal distribution. Categorical variables were evaluated using Chi-square test and numerical variables were evaluated using Independent samples *t* test, Mann-Whitney *U* test or Wilcoxon test. Kruskal-Wallis test was used to make comparisons between the disease severity groups and the control group. The correlations were determined by Spearman correlation analysis. Results with p values<0.05 were considered statistically significant.

Table 1
Demographic and clinical characteristics of the participants.

	HS, n = 26	Healthy controls, n = 24	*p*-values
Age			†0.961
mean (SD), years	35.12 (13.12)	34.92 (13.02)	
median (IQR), years	36.5 (23–45)	36.5 (20.25–45)	
Sex, n (%)			‡0.902
female	8 (30.8)	7 (29.2)	
male	18 (69.2)	17 (70.8)	
Smoking, n (%)			
Current smoker	16 (61.5)	8 (33.3)	‡0.046*
Non-smoker	10 (38.5)	16 (61.5)	
BMI, mean (SD), kg/m^2	29.32 (4.73)	25.47 (3.06)	§0.001**
Obesity (BMI ≥ 30), n (%)	14 (53.8)	3 (12.5)	‡0.002**
mHSS, mean (SD)	20.31 (7.89)		
HS-PGA, n (%)			
Minimal	4 (15.4)		
Mild	12 (46.2)		
Moderate	7 (26.9)		
Severe	3 (11.5)		
Age at onset, median (IQR), years	20.5 (14–32.75)		
Disease duration, median (IQR), years	9 (2.75–19)		
Family history (yes), n (%)	4 (15.4)		

BMI, Body mass index; *HS,* hidradenitis suppurativa; *HS-PGA,* Hidradenitis Suppurativa Physician's Global Assessment; *IQR,* interquartile range; *mHSS*, modified Hidradenitis Suppurativa Score.
†Mann-Whitney *U* test ‡Chi-square analysis §Independent samples *t* test.
*$p < 0,05$ **$p < 0,01$.

Table 2
Concentrations of serum markers.

	HS pre-treatment, n (%) Median (IQR)	Healthy controls, n (%) Median (IQR) / HS post-treatment (3 months), n (%) Median (IQR)	*p*-values
TNF-α (pg/mL)	n = 15 (57.7) 0.42 (0.08–1.25)	n = 13 (54.2) 0.25 (0.08–0.58)	†0.594
		n = 16 (61.5) 0.25 (0.08–1.25)	‡0.972
IL-1β (pg/mL)	n = 11 (42.3) 0.56 (0.28–0.84)	n = 10 (41.7) 0.70 (0–9.12)	†0.474
		n = 12 (46.2) 0.28 (0.28–0.99)	‡0.581
IL-17A (pg/mL)	n = 16 (61.5) 0.60 (0.43–0.94)	n = 11 (45.8) 2.32 (0.43–2.49)	†0.044*
		n = 17 (65.4) 0.43 (0.25–1.20)	‡0.372
IL-23 (pg/mL)	n = 26 (100) 17.95 (7.69–26.29)	n = 24 (100) 12.82 (6.73–22.76)	†0.360
		n = 26 (100) 13.46 (8.65–22.76)	‡0.492
hs-CRP (mg/L)	n = 26 (100) 16.53 (4.92–24.35)	n = 24 (100) 5.84 (1.56–12.53)	†0.010*
		n = 26 (100) 6.83 (2.01–15.84)	‡0.007**

HS, hidradenitis suppurativa; *IQR,* interquartile range; *TNF*, tumor necrosis factor; *IL*, interleukin; *hs-CRP*, high-sensitivity C-reactive protein.
†Mann-Whitney *U* test comparing the levels of markers between healthy controls and patients with HS. ‡Wilcoxon test comparing the pre- and post-treatment levels of markers among patients with HS.
*$p < 0,05$ **$p < 0,01$.

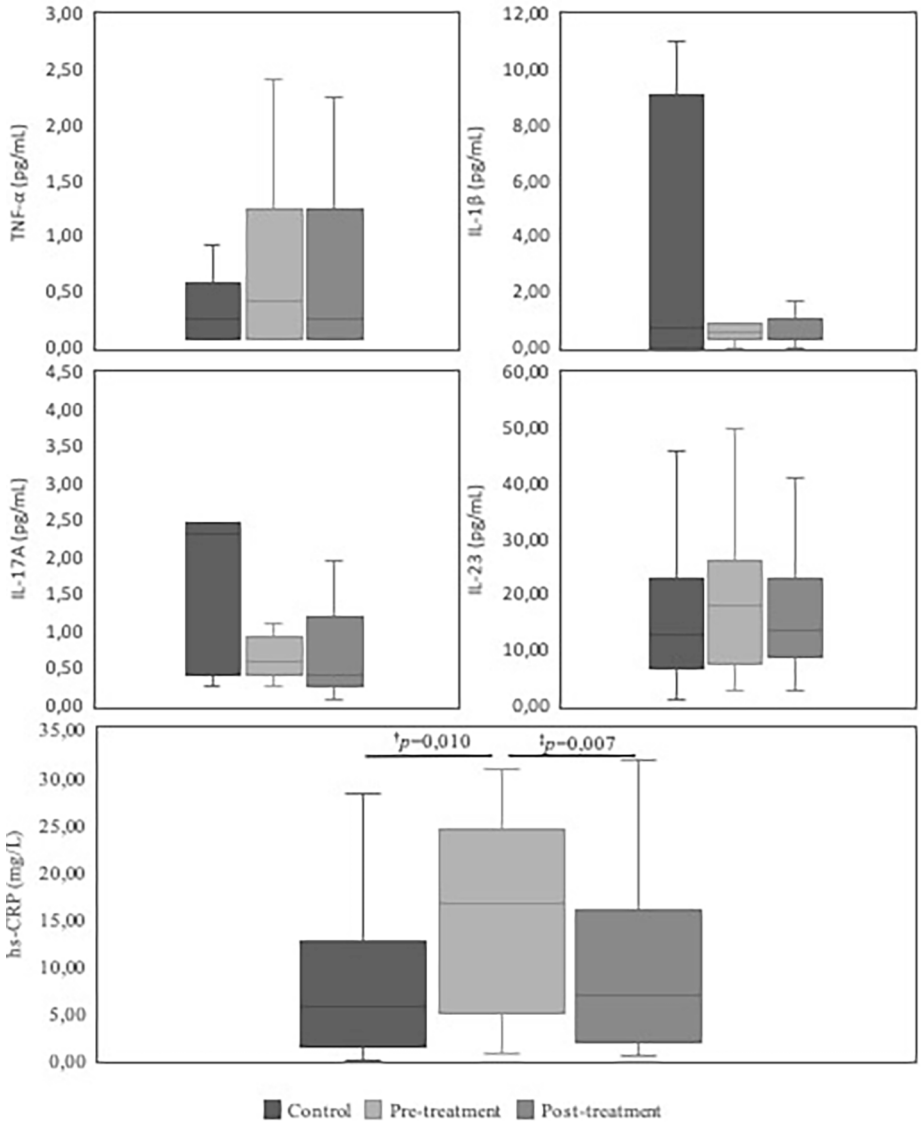


Fig. 1. The comparisons of serum TNF-α, IL-1β, IL-17A, IL-23 and hs-CRP concentrations between control group, pre- post-treatment state of the patients. The data are shown as non-outlier range (whiskers), interquartile range (box) and median (line). †Mann-Whitney *U* test. ‡Wilcoxon's test.

3. Results

3.1. Demographic and clinical characteristics

HS and control groups had, 8 females-18 males and 7 females-17 males. The mean age of the patients was 35.12 (±13.10). Among the patients with HS 61.4% (n = 16) were current smokers and 53.8% (n = 14) of them were obese. While smoking and obesity were more frequent in patients, BMIs were also higher than controls (p = 0,046; p = 0,02; p = 0,01). The demographic and clinical characteristics of the healthy controls and the patients with HS are summarized in Table 1.

Mean mHSS was 20.31 (±7.89) and 4 (15.4%) patient had minimal, 12 (46.2%) had mild, 7 (26.9%) had moderate and 3 (11.5%) had severe disease according to the HS-PGA. Median age of onset was 20.5 (IQR 14–32.75) and disease duration was 9 (IQR 2.75–19) years. 4 (15.4%) patients had a family history of HS.

3.2. Serum TNF-α, IL-1β, IL-17A, IL-23 and hs-CRP levels

Serum concentrations of the studied parameters in both groups and pre- and post-treatment levels of the patients are shown in Table 2. Serum TNF-α and IL-23 levels of HS patients were higher than controls and diminished following treatment, but these differences were not statistically significant. Also, no statistically significant difference was found in IL-1β and IL-17A pre-treatment levels of the patients and controls and the levels did not change significantly following treatment in HS group (Fig. 1).

The pre-treatment levels of hs-CRP in HS patients were significantly higher than the control group (p = 0.010) and also from post-treatment levels (p = 0.007) (Fig. 1).

Subgroups of patients treated with biological therapy (adalimumab) versus other treatments are compared and a non-statistically significant decrease in TNF-α and hs-CRP levels was observed in patients treated with adalimumab (n = 8). In patients treated with other treatments (n = 18), a decrease was found in all cytokine levels, which was also statistically significant for hs-CRP (p = 0,012) (Fig. 2).

The hs-CRP levels were analyzed according to smoking states and BMI values, which were not homogeneously distributed in the HS and control groups. When patients and controls evaluated together, hs-CRP levels did not differ significantly in smokers compared to non-smokers (p = 0.461). Similarly, the hs-CRP levels did not show a significant difference in overweight (BMI: 25–29.9) (p = 0.630), obese (BMI ≥ 30)

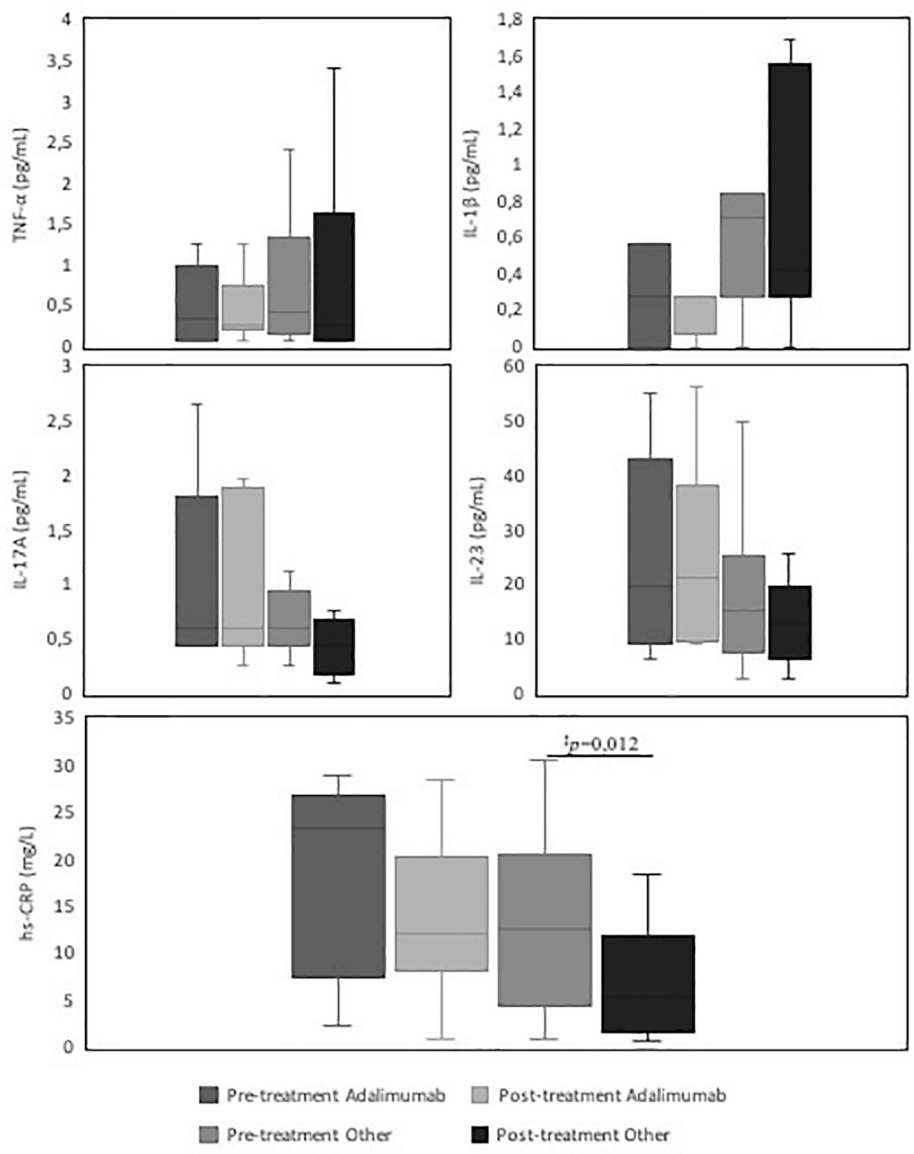


Fig. 2. The comparisons of serum TNF-α, IL-1β, IL-17A, IL-23 and hs-CRP concentrations between pre- and post-treatment state in adalimumab and other treatment subgroups. The data are shown as non-outlier range (whiskers), interquartile range (box) and median (line). ‡Wilcoxon's test.

($p = 0.215$) or BMI ≥ 25 ($p = 0,413$) individuals. In addition, hs-CRP levels were not correlated with BMI ($r_s = 0.197$, $p = 0.171$).

Since the number of patients in each subgroup was low, the patients were divided into two groups in terms of disease severity according to the HS-PGA, minimal-mild and moderate-severe, and the hs-CRP levels were compared between the control group and these two groups. Among 3 groups, hs-CRP levels were significantly different, and after pairwise comparisons, while the hs-CRP levels of the moderate-severe group were significantly higher than the control group ($p = 0.021$), there was no significant difference between the other two pairs. Also, hs-CRP levels were not correlated with mHSS ($r_s = 0.379$, $p = 0.056$).

4. Discussion

We have investigated serum levels of TNF-α, IL-1β, IL-17A and IL-23, which are thought to play a role in HS pathogenesis. Although insignificant, pre-treatment serum TNF-α and IL-23 levels were higher in HS group and decreased following treatment catching up the levels of healthy group. However, we were unable to find a statistically significant difference in TNF-α, IL-1β, IL-17A and IL-23 levels among HS patients and controls. Likewise, the difference between pre- and post-treatment levels of these cytokines were not statistically different.

Although the main initiating factor in pathogenesis of HS is not fully elucidated, follicular occlusion followed by the release of TNF-α, and IL-1β from local macrophages consequently leading to the activation of the innate immune system is hypothesized to be the initial step. These cytokines and their associated chemokines stimulate the innate immune system repeatedly causing the activation of the adaptive immune system [9]. Recent studies have shown induction of Th17 cells by IL-23 released from dendritic cells is to be important in etiology [10,11].

Several studies aiming to investigate circulatory levels of cytokines of this pathway resulted in varying results. Matusiak et al. demonstrated elevated serum TNF-α and IL-17 levels in two studies [12,13]. According to them, TNF-α levels were not associated with disease severity, while IL-17 levels were higher in more severe disease. In contrast, Blok et al. compared serum sIL-2R, TNF-α, IL-17A and IL-17F levels of 12 patients with both healthy controls and after ustekinumab treatment, and did not find any significant differences [14]. Jiménez-Gallo et al. compared serum levels of proinflammatory cytokines with controls in two studies [15,16]. They showed increased levels of IL-6, soluble TNF receptor

(sTNF-R) I, CRP and erythrocyte sedimentation rate (ESR) in the first and IL-6, IL-8, IL-10, IL-17A, sTNF-RII, CRP and ESR in the second study. Accordingly, current data does not point to a distinctive cytokine pattern. When we compare our results, the trend towards higher TNF-α levels of our patients is consistent with findings of Matusiak et al. Nevertheless, the inclusion of relatively mild patients and small sample size might be the reasons for the lack of significant differences in the levels of proinflammatory cytokines.

Studies evaluating the impact of treatment in the serum levels of proinflammatory cytokines are scarce. Montaudie et al. compared serum TNF-α, IL-1β, IL-6 and hs-CRP levels of 13 patients at the baseline and during infliximab treatment and found no significant difference [17]. However, Jiménez-Gallo et al. reported decreases in the levels of IL-1β, IL-6, IL-8, IL-10, IL-17A, sTNF-RI, sTNF-RII, CRP and ESR after adalimumab therapy [16]. We have found a trend towards decrease in TNF-α like Montaudie et al.

When we evaluated hs-CRP levels according to the disease severity, moderate-severe HS patients had significantly higher levels whereas hs-CRP levels of those with minimal-mild disease were comparable to controls. This finding supports hs-CRP to be a marker for disease activity. An interesting finding was alteration of hs-CRP levels not only with biologic treatments, but also with the use of antibiotics recommended by guidelines.

High hs-CRP is a surrogate for systemic inflammatory response which may potentially be related to comorbidities such as obesity. One may consider BMI as a confounder for hs-CRP levels as HS group and higher mean BMI. Thus, we have further analyzed hs-CRP levels in HS patients with obesity (BMI $\geq$ 30), and being overweight (BMI: 25–29.9) and could not found them to be different from the levels of patients with normal weight. Therefore, high hs-CRP levels seem to be related to inflammation.

The relatively low number of patients and their heterogeneous distribution according to disease severity are main limitations of our study. Also, we did not study HS lesions which may provide more specific data.

Based on the results of the present study and literature, it seems that there is insufficient data to suggest TNF-α, IL-1β, IL-17A and IL-23 as serum biomarkers in HS. Considering the possibility of multiple inflammatory pathways and interindividual variations, it is worthwhile to study the key cytokines in large groups including different subtypes of the disease. Such an approach will guide clinical studies and disease management. Since a reliable biomarker does not exist for HS, hs-CRP can be used for this purpose. In addition to clinical response, maintaining hs-CRP within normal limits, as an indicator for amelioration of systemic inflammation, may be a treatment goal.

CRediT authorship contribution statement

Gonca Saraç Öztürk: Conceptualization, Data curation, Writing - original draft. **Tülin Ergun:** Conceptualization, Methodology, Writing - review & editing, Supervision. **İrem Peker Eyüboğlu:** Investigation. **Mustafa Akkiprik:** Investigation.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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