Osteopontin Levels in Ocular Behçet's disease: A Controlled Study

Göz Tutulumu Olan Behçet Hastalığında Osteopontin Düzeyleri: Kontrollü Çalışma

Ayça Tuzcu[*] **Serdal Uğurlu**[**] **Gülnur Andican**[***] **Yılmaz Özyazgan**[****] **Hasan Yazıcı**[**]

[*] Aydın Adnan Menderes Üniversitesi Tıp Fakültesi, Biyokimya Anabilim Dalı, Aydın, Türkiye
[**] İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Romatoloji Anabilim Dalı, İstanbul, Türkiye
[***] İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Biyokimya Anabilim Dalı, İstanbul, Türkiye
[****] İstanbul Üniversitesi Cerrahpaşa Tıp Fakültesi, Göz Hastalıkları Anabilim Dalı, İstanbul, Türkiye

Başvuru Tarihi: 11 Temmuz 2020 **Kabul Tarihi:** 01 Eylül 2020

ÖZET

Amaç: Osteopontin (OPN), inflamatuvar ve otoimmün mekanizmalarla ilgisi bulunan bir sitokindir. Bu çalışmada, göz tutulumu olan Behçet hastalarında OPN'in rolünü değerlendirmek amaçlanmıştır. Göz tutulumu olan Behçet hastalarındaki OPN, İnterlökin-10 (IL-10) ve İnterlökin-12 (IL-12) düzeyleri, bir otoimmün hastalık olan sistemik lupus eritematozus (SLE) ve sağlıklı kontrol gruplarıyla kıyaslanmıştır.

Gereç ve Yöntem: OPN, IL-10 ve IL-12 düzeyleri, göz tutulumu olan 22 Behçet hastasında (önce üveit atağı sırasında, sonra remisyona girdiğinde olmak üzere iki defa), 18 SLE hastasında ve 18 sağlıklı bireyde ölçülmüştür.

Bulgular: OPN düzeyleri aktif ve inaktif üveyitli gruptaki Behçet ve SLE hasta gruplarında artmıştır. IL-10 ve IL-12 düzeyleri yalnızca SLE hasta grubunda anlamlı artış göstermiştir.

Sonuç: OPN düzeyleri sağlıklı kontrollere kıyasla Behçet hastalarında artmış olsa da, aktif ve inaktif üveyit dönemleri arasında anlamlı bir fark oluşturmamıştır. Aynı şekilde aktif üveyit dönemindeki Behçet hastaları ile SLE hastaları arasında da anlamlı bir fark bulunmamıştır. Böylece, Behçet hastalığının en azından göz tutulumunda, OPN'in önemli bir sitokin olmayabileceği öne sürülebilir.

Anahtar Kelimeler: Otoimmünite; Behçet hastalığı; IL-10; IL-12; Osteopontin; SLE; Uveyit.

Ayça Tuzcu : 0000-0002-5035-9711
Serdal Uğurlu : 0000-0002-9561-2282
Gülnur Andican : 0000-0002-5292-3574
Yılmaz Özyazgan : 0000-0002-0555-768X
Hasan Yazıcı : 0000-0001-7900-4378

Corresponding author: Ayça Tuzcu
Aydın Adnan Menderes Üniversitesi
Tıp Fakültesi, Biyokimya Anabilim Dalı,
Aydın, Türkiye
e-mail: aycaurhan@gmail.com

Ethical approval: Local ethics committee (11.04.2011 12817)

ABSTRACT

Purpose: Osteopontin (OPN) is a cytokine involved in inflammatory and autoimmune mechanisms. In this study, we aimed to investigate OPN role in eye involvement in Behçet's disease (BD). To assess OPN in eye involvement in BD by comparing OPN and other cytokine levels both in BD and in systemic lupus erythematous (SLE), an autoimmune disease, and in healthy controls.

Materials and methods: OPN, interleukin-10 (IL-10) and interleukin-12 (IL-12) levels were measured in 22 BD patients (once during an eye attack and once when the attack subsided) as well as 18 SLE patients and 18 healthy controls.

Results: The OPN levels were increased in SLE and in active and inactive Behçet's uveitis. The IL-10 and IL-12 were significantly increased only in SLE patients.

Conclusions: Although OPN levels in BD patients were significantly higher with healthy controls, no differences in OPN levels were observed between active-inactive Behçet's uveitis or between active Behçet's uveitis and SLE. This may suggest that OPN might not be an important cytokine at least in BD eye disease.

Keywords: Autoimmunity; Behçet's disease; IL-10; IL-12; Osteopontin; SLE; Uveitis.

INTRODUCTION

We investigated osteopontin (OPN) in eye involvement in Behçet's disease (BD) by comparing OPN and other cytokine levels both in active-and inactive Behçet's uveitis and in systemic lupus erythematous (SLE). OPN levels are known to be increased in SLE, a disease known to be autoimmune and there is still debate about the contribution of autoimmune versus autoinflammatory mechanisms in BD.

BD is a chronic, relapsing, multisystemic inflammatory disorder characterized by recurrent oral and genital ulcers and by ocular involvement (1). Several mediators are important in the associated uveitis characterized by periods of exacerbation and remission (2). T helper 1 (Th1) lymphocytes producing proinflammatory mediators (IL-2, IL-6, IL-8, IL-12, IL-17, IL-18, TNF-α and IFN-γ) are increased in BD (3-6).

OPN was initially isolated as one of the structural proteins of the bone tissue and is also known to be expressed in other tissues. It is involved in a number of biological processes (7, 8) like biomineralization, inflammation, dystrophic calcification, wound healing, granuloma formation, fibrosis, regulation of nitric oxide production, tumor metastasis, programmed cell death (apoptosis) and protection of cell viability (9). The levels of OPN are increased in various types of cancers and inflammatory diseases. Highly elevated expression of OPN in plasma is observed in autoimmune disorders such as multiple sclerosis, SLE, rheumatoid arthritis, atherosclerosis and other inflammatory diseases including cardiovascular disease, chronic obstructive pulmonary disease, inflammatory bowel disease, liver disease, and asthma (10). OPN is a relatively new cytokine and is thought to be pro-inflammatory. It mainly increases the level of pro-inflammatory cytokine interleukin-12 (IL-12) and decreases the level of anti-inflammatory cytokine interleukin-10 (IL-10) (10). However some studies suggest that OPN has an anti-inflammatory effect in the acute phase and a pro-inflammatory effect in the chronic phase of inflammatory diseases such as ulcerative colitis (11).

OPN promotes the Th1 and Th17 responses during chronic inflammation (11, 12). The Th17 lymphocytes produce large amounts of IL-17, IL-6, and TNF- α but decrease the level of IFN-γ (13). Elevated levels of IL-17 levels were reported in BD patients with active uveitis (14).

Because of its stimulatory role in Th-1-mediated immunity, OPN is also reported to be associated with autoimmunity (10). OPN

might also have a role as an auto-antigen for autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematous (SLE) (15, 16). It also exacerbates inflammation in experimentally-induced autoimmune uveitis in rats (17). Blockade of OPN with anti-OPN antibodies were proposed as therapeutic agents in diseases like rheumatoid arthritis, multiple sclerosis, autoimmune hepatitis, Crohn's disease, and atherosclerosis (18). They were shown to be useful in the treatment of experimental uveitis without causing severe side effects (19).

While there have been several studies of OPN in BD (20-22), only one study (20) was specifically conducted among BD patients with ocular disease. This showed that OPN levels were increased in BD patients with active uveitis.

Here, we again studied the OPN levels in BD uveitis during the active and inactive phases in the same patients. The OPN levels were also measured for the healthy controls, as well as the patients with active SLE as a diseased control group. The IL-10 and IL-12 levels (the former an anti-inflammatory and the latter a pro-inflammatory cytokine) were also measured. Finally, the associations between these and C-reactive protein (CRP) as well as the erythrocyte sedimentation rate (ESR) were assessed.

MATERIALS AND METHODS

We enrolled 22 patients diagnosed as Behçet's disease with ocular involvement and criteria fulfilling the International Study Group for Behçet's disease Criteria (23) as well as 18 SLE patients with active disease. Patients with severe extraocular involvement (vascular, neurological, joint problems etc.) and comorbid diseases (hypertension, diabetes mellitus, cancer, neurological and psychiatric disorders, serious systemic infection, chronic organ failure, genetic disorders) were excluded. The study was approved by the local ethics committee and written informed consents were received from all participants. Each BD patient was assessed twice by the same ophthalmologist for eye involvement: 1) during an active stage of uveitis and 2) three months after the attack during a remission period. Venous blood samples of all patients and healthy controls were studied in parallel and were collected in dry tubes and tubes containing EDTA. The samples were centrifuged at 1000 g for 15 minutes. Serum and plasma samples were placed in separate tubes immediately and stored at -80 º C until the time of analyses. Age, sex, duration of disease, frequency of uveitis attacks, drugs used, BD-related symptoms and/or signs (oral and genital ulcers, arthralgia, arthritis, skin lesions, thrombophlebitis, gastrointestinal involvement, neurological involvement)were also recorded at each visit by the rheumatologists. All BD patients used azathiopurine, cyclosporine, and prednisolone as systemic immunosuppressive medications. These medications decrease the disease activity and provided remission. The disease activity was assessed for each SLE patient using the SLE Disease Activity Index (SLEDAI). Patients with SLEDAI scores 4 or higher were defined as being in the active period and included in the study (24). A convenience control group was composed of 18 apparently healthy subjects working in Cerrahpaşa Medical Faculty matching with the study groups for age and gender. Serum IL-10, IL-12 levels and plasma OPN levels were measured using ELISA (Orgenium, eBioscience and Quantikine, respectively).

Statistical Analysis

Shapiro-Wilk test or Kolmogorov-Smirnov test was used to test the normality of distributions. A paired t-test was used for the variables with normal distribution, and the Wilcoxon Signed Ranks test was used for the variables that cannot be assumed to be normally distributed. A one-way ANOVA and Tukey's post hoc test were used to compare the patients with active Behçet's uveitis, SLE and healthy control groups. The Spearman correlation analysis was used to analyze the

relation between the parameters. Statistical Package for the Social Sciences (SPSS) was used for statistical analysis, and $p<0.05$ was considered to be statistically significant.

RESULTS

Demographic characteristics of the study groups such as age, gender and duration of disease were evaluated. 22 BD patients possessed different clinical characteristics: 20 patients had oral ulcers, 16 had genital ulcers, 12 were pathergy positive. All BD patients with eye disease had uveitis: 10 had panuveitis, 8 had posterior and 4 anterior uveitis. The extraocular manifestations of BD were in remission in both the initial examination and second sampling phase. Moreover in second sampling, the ocular and extraocular manifestations were in remission in all BD patients.

OPN

OPN levels were 67.29±24.29 ng/mL in the control group, 119.88±66.55 ng/mL in SLE patients, 107.04±45.15 ng/mL in patients with active Behçet's uveitis and 96.79±34.09 ng/mL in patients with inactive Behçet's uveitis, respectively (Figure 1).

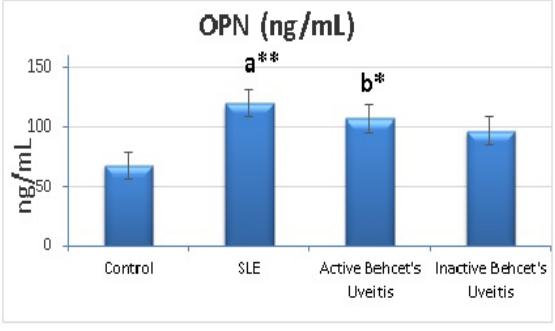

Figure 1. OPN levels

a = SLE vs healty controls (** $p<0.01$)

b = Active Behçet's uveitis vs healty controls (* $p<0.05$)

As seen in Figure 1, the OPN levels among the patients with active Behçet's uveitis and the patients with inactive Behçet's uveitis were significantly higher than the levels seen in healthy controls. This was also the case for the SLE patients relative to healthy controls. However, there were no statistically significant differences between the OPN levels of SLE patients when compared to that found in patients with active Behçet's uveitis. There were no differences between the OPN levels in active and inactive Behçet's uveitis (Table 2).

In addition, a negative correlation between age and OPN was found in patients with active Behçet's uveitisand in the healthy control group [r=-0.711 (p=0.001) and r=-0.474 (p=0.026)]. The OPN showed positive correlations with CRP and ESR levels in SLE patients [r=0.544 (p=0.020) and r=0.520 (p=0.027)].

IL-10

As seen in Table 1, the IL-10 levels were highest among the SLE patients. However there were no statistically significant differences between the levels in patients with active Behçet's uveitis and in healthy controls (Table 1). There were no differences between the levels inactive and inactive Behçet's uveitis (Table 2).

IL-12

IL-12 level differences were similar in distribution with the IL-10 levels between the groups.As seen in Table 1, the IL-12 levels were highest among the SLE patients. However there were no statistically significant differences between the levels in patients with active Behçet's uveitis and in healthy controls (Table 1). Also no differences were observed between the levels inactive and inactive Behçet's uveitis (Table 2).

CRP and ESR

CRP and ESR levels were highest among the SLE patients. There were no statistically significant differences between the levels in patients with active Behçet's uveitis and healthy controls (Table 1).

Table 1. OPN, IL-10, IL-12 levels in the healty controls, SLE and active Behçet's uveitis groups

	Active Behçet's uveitis (n=22) mean ± sd	**SLE (n=18) mean ± sd**	**Healty controls (n=18) mean± sd**	**p**
ESR (mm)	27.41±18.50	48.17±34.61	14.28±6,25	**a:** p<0.001 **b:** p=0.104 **c:** p<0.001
CRP (mg/L)	4.21±2.82	10.52±11.34	1.69±1.54	**a:** p<0.001 **b:** p=0.32 **c:** p<0.01
IL-10 (pg/mL)	2.22±1.54	5.43±4.81	1.09±0.85	**a:** p<0.001 **b:** p=0.88 **c:** p<0.01
IL-12 (pg/mL)	3.01±1.19	7.42±5.23	3.49±1.82	**a:** p<0.001 **b:** p=0.44 **c:** p<0.001
OPN (ng/mL)	107.04±45.15	119.88±66.55	67.9±24.29	**a:** p<0.01 **b:** p<0.05 **c:** p=0.68

ESR: erythrocyte sedimentation rates, CRP: c-reactive protein, IL-10: interleukin-10, IL-12: interleukin-12, OPN: osteopontin

a **= SLE vs healty controls**
b **= active Behçet's uveitis vs healty controls**
c **= active Behçet's uveitis vs SLE**

Table 2. OPN, IL-10 and IL-12 levels of patients with Behçet's uveitis during the active and remission periods

	Active (n=22) mean ± sd	**In remission (n=22) mean ± sd**	**p**
ESR (mm)	27.41±18.5	16.55±7.26	p<0.01
CRP (mg/L)	4.21±2.82	2.42±2.24	p<0.05
IL-10 (pg/mL)	2.22±1.54	2.24±2.03	p=0.946
IL-12 (pg/mL)	3.01±1.19	2.83±1.17	p=0.64
OPN (ng/mL)	107.04±45.15	96.79±34.09	p=0.235

ESR: erythrocyte sedimentation rates, CRP: c-reactive protein, IL-10: interleukin-10, IL-12: interleukin-12, OPN: osteopontin

DISCUSSION

During inflammation, OPN is synthesized from many different cell types involved in the inflammatory process including macrophages, endothelial cells, smooth muscle cells and fibroblasts. It modulates cytokine release and acts as a regulator of inflammation (25, 26). Osteopontin was mentioned as "another brick in the wall" in immune system (27) Chu et al. showed that OPN levels in patients with active Behçet's uveitis were significantly higher than the healthy control group as shown in our study. They concluded that the OPN levels of active BD patients were significantly higher than inactive BD patients (20). In our longitudinal design, even though the patients during the active stage of their uveitis had higher OPN levels versus healthy controls, there was no significant drop

during the remission period. On the other hand, the acute phase indices CRP and ESR significantly decreased during the remission this concurred with the fact that our BD patients were also in remission for any extraocular manifestation of the disease during the second blood collection. These observations suggest that OPN levels may not be good indicators of uveal tract inflammation in BD, but that they might be good indicators of inflammation in other organ systems during BD (21, 22). These suggest an apparent need for further work.

A Chinese study (20) of uveitis patients treated for at least a year, showed that an additional 3 months was needed before the investigators considered to be inactive. Perhaps coupling this long time treatment with a longitudinal design is needed. Ertürkler et al. showed that patients with BD were divided into active and inactive groups with regard to mucocutaneous and vascular involvement. The OPN levels were found to be significantly higher in patients with active BD versus a healthy control group as shown in our study (21). In another study, disease activity and the severity of Behçet patients were assessed using clinical scores and laboratory parameters. Plasma OPN levels in active and inactive BD patients were significantly higher than in control group. These findings were associated with disease activity, severity and vascular involvement (22).

In another study, Chu et al. investigated OPN in Vogt-Koyanagi-Harada (VKH) disease. VKH is a chronic granulomatous inflammatory relapsing disorder that causes uveitis. They found that OPN serum levels were significantly higher in patients with active VKH than in patients with inactive VKH or in healthy controls. They concluded that OPN may be relevant to the pathogenesis of uveitis in VKH (28). The fact that the OPN levels they measured were higher than those in our study may be due to their study design or to the pathogenesis of VKH disease. VKH uveitis may have other features in comparison with BD uveitis. This discrepancy might also attributable to differences between study designs. Chu et al. studied patients that had been treated for longer periods and samples that were taken three months after the medication had been stopped. You have right in your concerns regarding cytokine levels association with different systemic immunosuppressive medications, however we had used combination therapy, that is why we did not include any explanation concerning possible effects of certain medications on OPN levels in BD patients.

There is still controversy over (29) whether BD is an autoimmune disease. The frequency of vitiligo, Sjogren's and other autoimmune diseases is not increased in BD patients (30-33). Systemic Lupus Erythematosus (SLE) is a chronic multisystemic disease of autoimmune origin (16), Behçet's disease does not have the classical clinical features of autoimmunity such as anti-nuclear antibody (ANA) positivity, female dominance and association with other autoimmune diseases. There are certain human leukocyte antigen (HLA) alleles and haplotypes that are associated with autoimmune diseases. Alleles or haplotypes traditionally associated with autoimmune disease have not been found to go with BD. Also, almost all autoimmune diseases are associated with some B cell hyperreactivity to some extent in the form of either organ-specific (i.e. antithyroid) or non-organ-specific (i.e. antinuclear) antibodies. This is not valid for BD. Organ or non-organ-specific antibodies are not found in any consistency in patients with BD. On the other hand, there is no classical cytokine pattern indicative of a autoimmune disease to compare with the findings observed in BD (32) Immunological differences between SLE and BD may cause different levels of OPN measured in our study.

For this reason, we included a diseased control group of active SLE patients in the current study. Interestingly, it was only among these patients that OPN, IL-10 and IL-

12 levels were significantly elevated. Spinelli at al showed that OPN could be considered a biomarker of renal involvement in SLE, without differentiating between active and remission lupus nephritis (Y 34) Also, In a cohort study conducted in 11 countries (North America, Europe and Asia) they investigated OPN associated significantly with lupus nephritis and with raised SLE disease activity at enrollment (Z 35). Therefore, we speculated that SLE may differ from BD in that it has a different inflammatory pathway.

There were no significant differences in the levels of IL-10 and IL-12 among the BD patients in the active stage and in remission. Similarly, Hurmeric et al. (36) showed no difference in IL-10 levels between patients with active Behçet's uveitis, patients with inactive Behçet's disease, and the control group. This is mainly based on genetic data (37). There has been recent interest in the role of IL-10, an anti-inflammatory cytokine, in the pathogenesis of BD. The limited number of patients with primarily eye disease in our study supports the conclusions of Hurmeric et al (36).

Karikuri et al. (38) showed that OPN levels had no differences between male and female. In our study, we choosed active SLE patients as a diseased control group since SLE hasa autoimmune origin. Altough BD patients showed a male dominance, many of the SLE patients were female so, more studies are needed to understand gender effects on cytokine levels.

IL-12 was previously found to be increased in active BD patients (5). In our patients, the IL-12 levels were not significantly higher. This difference may be due to the study design because in our study we excluded patients with extraocular manifestations. Also, the pathogenetic mechanisms in BD might differ across disease manifestations (39).

Our study had some limitations. We did not have the opportunity to study the SLE patients during a remission as we did BD patients. Furthermore it would have been more informative if we had studied the same BD cases in attacks of other extraocular BD manifestations. Our study included 22 BD patients with ocular involvement. While this is relatively limited, similar studies from China and Egypt (5, 20) included 25 and 30 patients, respectively. The findings from these studies needed to be verified by further research.

OPN is a recently discovered cytokine. We found that it is elevated in patients with Behçet's uveitis. However, no significant difference was detected between patients in periods of remission and manifest disease. There were no significant differences in OPN levels between Behçet patients with active uveitis and patients with SLE. Therefore we speculated that OPN does not play a pivotal role in ocular manifestation of BD though this might not be the case for the other manifestations because of the heterogeneous nature of BD. Further studies are required to determine the effects of OPN in inflammation and autoimmunity.

KAYNAKLAR

1. Yazici Y, Yurdakul S, et al. Behçet's Syndrome. CurrRheumatol Rep. 2010; 12(6): 429-35.
2. Onder M, Gurer MA. The multiple faces of Behcet's disease and its aetiological factors. J Eur Acad Dermatol Venereal. 2001; 15: 126-36.
3. Evereklioğlu C. Current concepts in the etiology and treatment of Behçet disease. Surv Ophthalmol. 2005; 50: 297-350.
4. Doğanavşargil E, Keser G. BehçetHastalığı. T Klin J Int Med Sci. 2005; 1: 80-91.
5. Hamzaoui K, Hamzaoui A, et al. Cytokine profile in Behçet's disease patients. Scand J Rheumatol. 2002; 31: 205-10.
6. Ilhan F, Demir T, et al. Th1 polarization of the immune response in uveitis in Behçet's disease. Can J Ophthalmol. 2008; 43: 105-8.
7. Yasui T, Sato M, et al. Effects of citrate on renal stone formation and osteopontin in a rat urolithiasis model. Urol Res. 2001; 29: 50-5.
8. Sodek J, Ganss B, et al. Osteopontin. Crit Rev Oral Biol. Med. 2000; 11: 279-303.

9. Mazalli M, Kipari T, et al. Osteopontin--a molecule for all seasons. Q J Med. 2002; 95: 3-13.
10. Wang KX, Denhardt DT. Osteopontin: Role in immune regulation and stress responses. Cytokine Growth Factor Rev. 2008; 19: 333-45.
11. Heilmann K, Hoffmann U, et al. Osteopontin as a two-sided mediator of intestinal inflammation. J Cell Mol Med. 2009; 13: 1162-74.
12. Zheng Y, Wang Z, Deng L, et al. Osteopontin promotes inflammation in patients with acute coronary syndrome through its activity on IL-17 producing cells. EurJ Immunol. 2012; 42(10): 2803-14.
13. Angrish CL, Chen Y, Blumenschein WM, et al. IL-23 drives a pathogenic T cell population that induces autoimmune inflammation. J Exp Med. 2005; 201(2): 233–40.
14. Chi W, Zhu X, Yang P, et al.Upregulated IL-23 and IL-17 in Behçet patients with active uveitis. Invest Ophthalmol Vis Sci. 2008; 49(7): 3058-64.
15. Yamamoto N, Nakashima T, et al. Successful treatment of collagen-induced arthritis in nonhuman primates by chimeric anti-osteopontin antibody. IntImmunopharmacol. 2007; 7: 1460-70.
16. Kaleta B. Role of Osteopontin in Systemic Lupus Erythematosus. Arch. Immunol. Ther. Exp. 2014; 62(6): 475-82.
17. Kitamura M, Iwabuchi K, et al. Osteopontin aggravates experimental autoimmune uveoretinitis in mice. J Immunol. 2007; 178: 6567-72.
18. Morimoto J, Kon S, et al. Osteopontin; as a target molecule for the treatment of inflammatory diseases. Targets. 2010; 11: 494-505.
19. Iwata D, Kitamura M, et al. Prevention of experimental autoimmune uveoretinitis by blockade of osteopontin with small interfering RNA. Exp Eye Res. 2010; 90: 41-8.
20. Chu M, Yang P, et al. Behçet's disease exhibits an increased osteopontin serum level in active stage but no association with osteopontin and its receptor gene polymorphisms. Human Immunology. 2011; 72: 525-29.
21. Erturkler E, Cicek D, et al. Plasma osteopontin levels in patients with Behcet's disease and psoriasis.Eur J Dermatol. 2011; 21: 203-8.
22. Bassyouni IH, El-Wakd MM, et al. Soluble levels of osteopontin in patients with Behcet's disease: Association with disease activity and vascular involvement. J ClinImmunol. 2013; 33: 361–7.
23. O'Neill TW, Rigby AS, et al. Validation of the international study group criteria for Behcet's disease. Br J Rheumatol. 1994; 33: 115-7.
24. Golbus J, McCune WJ. Lupus nephritis. Classification, prognosis, immunopathogenesis and treatment. Rheum Dis Clin North Am. 1994; 20: 213-42.
25. Ashkar S, Weber GF, et al. Eta-1 (osteopontin): An early component of type-1 (cell- mediated) immunity. Science 2000; 4: 860-4.
26. Lampe MA, Patarca R, et al. Polyclonal B cell activation by the eta-1 cytokine and the development of systemic autoimmune disease. J Immunol. 1991; 47: 2902-6.
27. Caputo S, Bellone M. Osteopontin and the immune system: another brick in the wall. Cell Mol Immunol. 2018;15(4):405-407. doi: 10.1038/cmi.2017.94.
28. Chu M1, Yang P, Hu R, et al. Elevated serum osteopontin levels and genetic polymorphisms of osteopontin are associated with Vogt-Koyanagi-Harada disease.Invest Ophthalmol Vis Sci. 2011; 52(10):7084-9.
29. Dirsekenli H. Autoimmunity vs autoinflammation in Behcet's disease: Do we oversimplify a complex disorder? Rheumatology. 2006; 45: 1461–5.
30. Oran M, Hatemi G, Tasli L, et al. Behçet's syndrome is not associated with vitiligo. ClinExpRheumatol. 2008; 26: 107-9.
31. Günaydin I, Ustündağ C, Kaner G, et al. The prevalence of Sjögren's syndrome in Behçet's syndrome. J Rheumatol. 1994; 21(9): 1662-4.
32. Yazici H. The place of Behçet's syndrome among the autoimmune diseases. Int Rev Immunol. 1997; 14(1): 1-10.
33. Yazici H, Fresko I. Behçet's disease and other autoinflammatory conditions: What's in a name? ClinExpRheumatol. 2005; 23: 1-2.
34. Spinelli F, Garufi C, Truglia S, et al. The role of osteopontin as a candidate biomarker of renal involvement in systemic lupus erythematosus. Clin Exp Rheumatol Nov-Dec 2019;37(6):899-905.
35. Wirestam L, Enocsson H, Skogh T et al. Osteopontin versus disease activity and damage accrual in recent-onset systemic lupus erythematosus: Results from the Systemic Lupus International Collaborating Clinics Inception Cohort. J Rheumatol. 2019; 46(5): 492–500.
36. Hurmeric V, Erdem Ü, et al. Üveitli olgularda sitokin profilinin karşılaştırılması. Gülhane Tıp Dergisi. 2006; 48: 151-6.
37. Remmers EF, Cosan F, Kirino Y, et al. Genome-wide association study identifies variants in the MHC class I, IL10, and IL23R-IL12RB2 regions associated with Behçet's disease.Nat Genet. 2010; 42(8): 698-702.
38. Kariuki SN, Moore JG, Kirou KA, et al. Age-andgender-specificmodulation of serum osteopontinand interferon-α byosteopontingenotype in systemiclupuserythematosus. GenesImmun. 2009; 10(5): 487-94.
39. Yazici H, Ugurlu S, Seyahi E, et al. Behçet syndrome: Is it one condition? Clin Rev Allergy Immunol. 2012; 43(3): 275-8