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# Clinical characteristics of avascular necrosis in patients with Behçet disease: a case series and literature review

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## Abstract

Avascular necrosis (AVN), also known as osteonecrosis, is characterized by death of the osteocytes due to inadequate blood supply caused by various mechanisms. The hip is the most common affected joint followed by knee. Incidence of AVN in rheumatic diseases is variable and high corticosteroid (CS) therapy is a known major risk factor for development of AVN. Data on the AVN in Behçet disease (BD) are limited. The purpose of this study is to examine the clinical and treatment characteristics of BD patients with diagnosis of AVN. Retrospective medical records of 337 BD patients were reviewed. Nine BD patients with AVN were detected. The clinical data of these patients with AVN have been reviewed. All patients had MRI of the symptomatic joints compatible with AVN. All of the nine patients who were diagnosed with AVN were male. Median duration of BD was 7 years. Median time between diagnosis of BD and detection of AVN was 3 years (1–16 years). Multiple joints were involved in seven patients. Six patients had bilateral knee AVN. Six patients had vascular BD. The median time interval between initial CS dose and AVN development was 24 months (range = 2–100). The median highest daily CS dose was 64 mg/day (range = 32–80) and median cumulative CS dose prior to AVN was 18 g. All of patients had intravenous pulse steroids. CS treatment, smoking and vascular involvement may predispose to AVN in patients with BD. According to this cohort, AVN in BD frequently tended to be in the knee joint and bilateral.

**Keywords** Behçet disease · Avascular necrosis · Corticosteroid · Multifocal involvement

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## Introduction

Avascular necrosis (AVN), also known as osteonecrosis, is characterized by death of the osteocytes. Although the pathogenesis of AVN is not fully understood, the pathogenesis is believed to be multifactorial and interruption of blood supply is the main mechanism of AVN. Alcohol abuse, corticosteroid (CS) use, altered lipid metabolism, sickle cell anemia, coagulopathy, trauma, Gaucher disease, and connective tissue disorders are risk factors for the development of AVN [1]. The exact frequency of AVN is unknown. There are approximately 20,000–30,000 patients newly diagnosed with AVN each year in the United States [2]. In the German-speaking countries, AVN of hip has an incidence of 0.01% [3]. The prevalence of AVN in hip joints was reported as 0.725% in the Chinese population [4]. AVN is also observed in rheumatologic disorders, especially in systemic lupus erythematosus (SLE). The reported prevalence of AVN in patients with SLE changes between 10 and 44% [5, 6].

The clinical manifestation is variable, ranging from asymptomatic radiologic incidental finding to severe pain, joint damage and limitation in mobility and collapse of joint. Hip is the most commonly affected joint, followed by knee [7]. AVN may require surgery and need of tapering CS dose. Thus, it constitutes an additional challenge in the management of underlying disease. Furthermore, for a better outcome in AVN, early diagnosis and proper management in high risk patients is crucial. AVN by itself is underlying reason in approximately 10% of all total hip replacements [8]. CS therapy is a known major risk factor for development of AVN [9]. In a study investigating incidence of AVN in hips and knees of patients who received corticosteroid therapy for various inflammatory and non-inflammatory disorders, the incidence was 37% in systemic lupus erythematosus (SLE), 27% in polymyositis/dermatomyositis, 14% in vasculitis syndromes, 45% in adult-onset Still's disease, 33% in systemic sclerosis, 25% in granulomatosis with polyangiitis and 0% in BD [10]. Exact incidence and prevalence of AVN in BD is largely unknown since no comprehensive study evaluated AVN in patients with BD.

BD is a chronic, multi-system, vasculitic disorder [11]. BD has acute temporary manifestations, such as oral aphthous ulcers, genital ulcers, arthritis which are usually resolve without a chronic sequela. However pan-uveitis, vascular and central nervous system (CNS) involvements usually results in severe organ damage, such as vision loss, chronic post-thrombotic syndrome, chronic progressive neuro-Behçet disease (neuro-BD) and brainstem atrophy [12]. AVN is also a chronic clinical entity observed in BD.

Although CSs are mainstay of the treatment in these major organ/system involvements of BD which has potential morbidity and mortality, AVN is rarely reported in patients with BD in the literature when compared to SLE and other rheumatologic disorders [13–19]. The limited published data about AVN in patients with BD may be due to masking effects of other rheumatologic symptoms like arthritis. Another reason may be due to asymptomatic nature of AVN in some patients which leads to underestimation of AVN in BD patients. To prevent underestimation of AVN in BD, it is important to define its clinical features. In this study, we evaluated clinical and treatment characteristics of nine BD patients with diagnosis of AVN.

## Materials and methods

We retrospectively reviewed the medical records of 337 patients with BD who followed at the outpatient tertiary rheumatology clinic of Gazi University Hospitals between 2011 and 2018. Nine patients with diagnosis of AVN were detected. The diagnosis of BD was made according to the International Study Group (ISG) criteria [20]. Demographic characteristics, duration of disease (years), the time between development of AVN and diagnosis of BD (years), history of smoking, surgery due to AVN, the site of AVN confirmed by magnetic resonance imaging (MRI) were defined. BD patients were classified as ocular, mucocutaneous, vascular, neurologic involvement and arthritis according to their clinical manifestations. The dominant organ involvement was defined as type of involvement that primarily determined the treatment decision.

Antinuclear antibody (ANA), anti-cardiolipin (aCL) IgM and IgG (U/ml), anti-β2 glycoprotein I (aB2-GPI) IgM and IgG antibodies (U/ml), serum total cholesterol (T Chol, 0–200 mg/dl), low density lipoprotein (LDL, 0–130 mg/dl), triglyceride (TG, 0–150 mg/dl), erythrocyte sedimentation rate (ESR, 0–20 mm/h) and C-reactive protein (CRP, 0–5 mg/L) levels at the time of diagnosis of AVN were recorded. Acquired and congenital hypercoagulability tests were performed in patients with vascular involvement.

We also evaluated CS treatment of patients as following; highest daily CS dose (mg/day), age at initial CS treatment was initiated, the time interval between initial CS administration and diagnosis of AVN (months), history of pulse CS administration, cumulative CS dose (mg) before diagnosis of AVN.

Other risk factors for AVN, including trauma, alcohol consumption, hemoglobinopathy, sickle cell anemia, coagulopathy, myeloproliferative diseases, leukemia and lymphoma, HIV infection, renal failure, inflammatory bowel diseases were also evaluated.

### Search strategy

A literature review was performed for manuscripts from 1978 to November 30th, 2018 to identify BD patients with AVN. The search was performed in two electronic databases (MEDLINE/PubMed and Scopus) using the following keywords: "Behçet", "Behçet's", "Behcet", "Behcet's", "osteonecrosis", "aseptic necrosis", "avascular necrosis" and "femoral head necrosis". We included all manuscripts (case reports, randomized controlled trials, case control, cohort, or cross-sectional studies) related with BD and AVN. Exclusion criteria were: manuscripts which are not accessible in full-text, publication in languages other than English, case reports characterized by not definitely proven BD and manuscripts which do not document clinical characteristics of AVN in BD patients. After analysis, we identified seven manuscripts about AVN in Behçet's disease. Six out of seven manuscripts were case reports and the other one was a study that evaluates the frequency of arthritis in Behçet's disease. In latter study, three cases of AVN were reported. Aforementioned study and six case reports were included in the final analysis, in addition to our study [13–15, 17–19, 21] (Tables 1, 2).

**Table 1** Summary of published cases of avascular necrosis in Behçet disease

| References | Patient no | Age, (years), sex | Duration of disease | Dominant organ involvement | Time between diagnosis of BD and AVN, (months) | Site of AVN detected by MRI | History of surgery due to AVN | Smoking during AVN diagnosis | Drugs prior to AVN | Current treatment | aCL IgG, IgM levels (U/ml) | aB2-GPI IgM, IgG levels (U/ml) | LDL, TG, T Chol levels | ESR, CRP levels |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Lin et al. [13] | 1 | 49, F | 6 years | na | 6 years | Bilateral hip and left knee | No | na | AZA | na | na | na | na | na |
| Ersöz et al. [14] | 1 | 66, F | 10 years | Neuro-BD | 10 years | Right hip | No | na | AZA | na | na | na | na | na |
| Essaadouni et al. [15] | 1 | 26, F | 3 years | Neuro-BD | 3 years | Unilateral hip | No | na | AZA | Tocilizumab-mab | na | na | na | na |
| Polat et al. [17] | 1 | 38, F | 7 months | Ocular | 7 | Bilateral knee | Left knee, debridement and curettage of the dead bone and bone grafting | na | AZA | AZA | (–) | na | na | ESR:60 CRP:68 |
| Chang et al. [18] | # 1 | 45, F | 0[a] | Mucocutaneous | 0 | Left knee | No | No | No drug | Colchicine | IgG:18 IgM: (–) | na | T Chol:202 | ESR:10 CRP:neg |
| | # 2 | 30, M | 2 and half years[b] | Neuro-BD and ocular | 30 | Right hip | Right hip, total joint arthroplasty | na | AZA, CsA | CsA | IgM:15 IgG: (–) | na | T. Chol: 154 | ESR:7 CRP: < 0.8 |
| Varoglu et al. [19] | 1 | 36, M | 1 year | Neuro-BD | 12 | Bilateral hip | Yes (the type of surgery wasn't defined) | na | No drug | na | na | na | na | na |
| Vaiopoulos et al. [21] | AVN in three male patients with diagnosis of BD (left hip, right hip and both hips). One of these patients underwent arthroplasty. Other clinical characteristics of these patients were not defined separately from other patients | | | | | | | | | | | | | |

*aB2-GPI* anti-B2 glycoprotein I ($n = 0$–10 U/ml), *aCL* anti-cardiolipin ($n = 0$–10 U/ml), *ADA* adalimumab, *AVN* avascular necrosis, *AZA* azathioprine, *CRP* C-reactive protein (0–5 mg/L), *CsA* cyclosporine, *ESR* erythrocyte sedimentation rate (0–20 mm/h), *LDL* low density lipoprotein (60–130 mg/dl), *MRI* magnetic resonance imaging, *Neuro-BD* neurobehçet disease, *na* not available, *T. Chol* total cholesterol (0–200 mg/dl), *TG* triglyceride (0–150 mg/dl)

[a]The diagnosis of BD and AVN was concurrent

[b]Although patient had symptoms of BD, such as oral aphthous and genital ulcer, erythema nodosum and uveitis for 5 years she had a delayed diagnosis of BD

**Table 2** Published cases of corticosteroid administration in Behçet disease patients with avascular necrosis

| References | Patient no | Body weight (kg) | Highest daily CS dose given | Pulse steroid administration schedule | Time interval between initial CS dose and AVN development | Cumulative CS dose prior to AVN (mg) |
|---|---|---|---|---|---|---|
| Lin et al. [13] | 1 | na | na | na | na | na |
| Ersöz et al. [14] | 1 | na | na | na | na | na |
| Essaadouni et al. [15] | 1 | na | 1 mg/kg | 1000 mg for 3 days[a] | na | na |
| Polat et al. [17] | 1 | na | 1 mg/kg | No CS pulse | 7 months | na |
| Chang et al. [18] | #1 | na | No CS | No CS pulse | Simultaneously | 0 |
| | #2 | na | na | na | 3 years | na |
| Varoglu et al. [19] | 1 | na | na | 1000 mg for 7 consecutive days | 12 months | na |
| Vaiopoulos et al. [21] | 3 | na | na | na | na | na |

*AVN* avascular necrosis, *CS* corticosteroid, *na* not available

[a]Patient had received two cycles of pulse steroid. The first cycle consists of a 3-day, 1000 mg/day intravenous (IV) infusion, second cycle was not well characterized

### Statistical analysis

Statistical analyses were performed using the SPSS software version 22. Categorical variables are presented as numbers and percentages. Continuous variables were presented as medians and ranges.

## Results

All of patients in our study were male. The dominant clinical manifestation was vascular in five patients, ocular in two patients, concomitant vascular–neurologic in one and ocular–neurologic in the other patient. The median age at the onset of BD was 25 years (range 16–57) and for AVN the median age was 35 years (range 17–60). Median duration of BD was 7 years (range 4–17). Median time between diagnosis of BD and diagnosis of AVN was 3 years (range 1–16) (Table 3).

In the present study, ANA was positive in three patients and aCL IgM and IgG and aB2-GPI IgM and IgG level was slightly above normal in two patients. Lipid profile at the time of diagnosis of AVN was available in four patients. One of these patients had elevated LDL and T. Chol levels, 204 mg/dl and 273 mg/dl, respectively. Another patient had slightly elevated TG level of 185 mg/dl. Median CRP and ESR were 13 mg/l (range 3–100) and 32 mm/h (range 3–76) at the time of diagnosis of AVN, respectively. Azathioprine (AZA) and cyclophosphamide (CYC) were the most commonly used immunosuppressive agents (Table 3). Except for one patient all were active smokers at the time of diagnosis of AVN.

We observed development of AVN in 20 joints (12 knee, 7 hip and 1 metacarpophalangeal) of nine patients. Multiple joints were involved in seven patients. Knee was the most commonly affected joint which was observed in six patients and in all of these both knees were affected from AVN. Hips were the second most commonly affected joint and the site was bilaterally affected in two patients, whereas unilateral in three of them. One patient had small joint AVN of the left third metacarpophalangeal joint along with knee and hip joints.

The median time interval between initial CS dose and AVN diagnosis was 24 months (range 2–100). The median highest daily CS dose was 64 mg/day (range 48–80) and median cumulative CS dose prior to AVN was 18 g (range 6–21). All of patients had multiple intravenous pulse steroid administration, but one patient received only a single dose of 500 mg pulse CS (Table 4). Three patients had needed of joint surgery due to AVN (Table 3).

## Discussion

In the present study, we evaluated the clinical characteristics of AVN in nine patients with BD, which has quite limited data. When compared to previous published cases, this study comprehensively evaluated clinical, treatment and laboratory characteristics and had the highest number of BD patients with AVN.

Corticosteroid use is associated with osteonecrosis in a dose-related fashion in adult patients with chronic inflammatory disorders [22]. All of patients who had had major organ involvements of BD had received CS in our cohort. There are a few case reports with use of CS prior to diagnosis of AVN in BD patients, but they were unable to provide details of the dose of CS [17, 19]. In this study, eight out of nine patients had a cumulative CS dose of more than 10 g and all of them had multiple intravenous (IV) pulse CS administrations. Most of patients also had oral daily CS dose of more

**Table 3** Baseline characteristics of nine male patients with Behçet disease and avascular necrosis in our cohort

| No. | Age, (years) | Duration of disease, (years) | Dominant organ involvement | Time between diagnosis of BD and AVN, (years) | Site of AVN detected by MRI | History of surgery due to AVN | Smoking during AVN diagnosis | Drugs prior to AVN | Current treatment | aCL IgG, IgM levels (U/ml) | aB2-GPI IgM, IgG levels (U/ml) | LDL, TG, T Chol levels | ESR, CRP levels |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 37 | 13 | Vascular and neuro-BD | 8 | Bilateral knee and hip | Right knee and left hip core decompression | Yes (10 pack-years) | AZA, CYC | IFN | Negative | Negative | LDL:129<br>TG:145<br>T Chol:203 | ESR:20<br>CRP:13 |
| 2 | 37 | 7 | Vascular | 2 | Bilateral knee, left hip, left 3rd MCP | No | Yes (9 pack-years) | AZA, CYC | AZA | Negative | Negative | LDL:103<br>TG:100<br>T Chol:163 | ESR:3<br>CRP:10 |
| 3 | 62 | 5 | Vascular | 3 | Right hip | No | Yes (16 pack-years) | AZA, CYC | AZA | Negative | Negative | na | ESR:48<br>CRP:16 |
| 4 | 19 | 3 | Ocular | 1 | Bilateral knee | No | No | AZA, CsA, IFN, IFX | IFX | Negative | Negative | na | ESR:11<br>CRP:7 |
| 5 | 39 | 14 | Neuro-BD and ocular | 10 | Bilateral knee | No | Yes (32 pack-years) | AZA, CsA, IFN, IFX ADA | ADA | Negative | Negative | LDL:83<br>TG:185<br>T.Chol:156 | ESR:48<br>CRP:100 |
| 6 | 43 | 4 | Vascular | 3 | Left hip | Left hip core decompression | Yes (28 pack-years) | AZA, CYC | MMF | Negative | Negative | na | ESR:33<br>CRP:7 |
| 7 | 44 | 17 | Ocular | 16 | Bilateral hip | Right hip core decompression | Yes (24 pack-years) | AZA, CsA | AZA | IgG:12<br>IgM:11 | Negative | na | ESR:76<br>CRP:100 |
| 8 | 33 | 14 | Vascular | 14 | Bilateral knee | No | Yes (15 pack-years) | CYC, AZA | IFX | Negative | Negative | LDL:204<br>TG:127<br>T.Chol:273 | ESR:9<br>CRP:3 |
| 9 | 25 | 4 | Vascular | 1 | Bilateral knee | No | Yes 2 (pack-years) | IFN, CYC | AZA | IgM:18<br>IgG:16 | Negative | na | ESR:32<br>CRP:57 |

*aB2-GPI* anti-B2 glycoprotein I ($n=0$–10 U/ml), *aCL* anti-cardiolipin ($n=0$–10 U/ml), *ADA* adalimumab, *AVN* avascular necrosis, *AZA* azathioprine, *CRP* C-reactive protein (0–5 mg/L), *CsA* cyclosporine, *CYC* cyclophosphamide, *ESR* erythrocyte sedimentation rate (0–20 mm/h), *IFN* interferon, *IFX* infliximab, *LDL* low density lipoprotein (60–130 mg/dl), *MMF* mycophenolate mofetil, *MRI* magnetic resonance imaging, *Neuro-BD* Neuro-Behçet disease, *na* not available, *T. Chol* total cholesterol (0–200 mg/dl), *TG* triglyceride (0–150 mg/dl)

**Table 4** Summary of corticosteroid administration in nine male patients with Behçet disease and avascular necrosis in our cohort

| No | Body weight (kg) | Highest daily CS dose, (mg/day) | Pulse steroid administration schedule | Time interval between initial CS dose and AVN development (months) | Cumulative CS dose prior to AVN (g) |
|---|---|---|---|---|---|
| 1 | 80 | 64 | 1000 mg/month, 8 cycles | 24 | 18 |
| 2 | 80 | 80 | 1000 mg/month, 8 cycles | 30 | 18.4 |
| 3 | 71 | 48 | 500 mg/q2w, 8 cycles | 27 | 14.2 |
| 4 | 74 | 80 | Single 500 mg infusion | 20 | 6 |
| 5 | 78 | 60 | 1000 mg/month, 5 cycles | 30 | 11 |
| 6 | 65 | 64 | 1000 mg for 3 consecutive days/2 cycles | 24 | 21 |
| 7 | 57 | 60 | 1000 mg/day, 3 cycles | 100 | 19 |
| 8 | 65 | 64 | 1000 mg for 7 consecutive days | 2 | 10 |
| 9 | 66 | 64 | 1000 mg/month, 8 cycles | 24 | 18 |

*AVN* avascular necrosis, *CS* corticosteroid

than 60 mg. This suggest us dose-dependent relationship with development of AVN and CS use. Hence, pulse therapy and high dose daily CS may constitute important risk factors for development of AVN in BD patients. In one patient, the time interval between the CS treatment and AVN diagnosis was only 2 months and the administered CS dose in these 2 months was 10 g due to refractory vascular BD. The short time interval between CS administration and development of AVN can be explained with many ways. The initial high glucocorticoid dose may be associated with development of AVN, as observed in SLE [6, 23, 24]. Smoking might be another facilitating factor, because the patient had had a history of 15 pack-years smoking [25]. Another reason may be related with the type of organ involvement (vascular) of BD. In literature, one BD patient without previous use of CS had diagnosis of AVN in unilateral knee joint [18]. This may postulate different mechanisms involved in pathogenesis of AVN in BD, other than CS.

Joint involvement of AVN differs between diseases. In non-SLE diseases, AVN tends to be in femoral head, but in SLE it tends to be in knees and multifocal [5, 6]. In reported cases of BD patients, most of patients had AVN of hip joints and unifocal involvement was more frequent than multifocal involvement (Table 1). In contrast to previous reports, in our study, we observed that AVN in knee joints was higher than hip joints in patients with BD, like SLE and most of patients had multifocal involvement of joints. Thus, it may be advisable to further investigate other knee and hip joints after diagnosis of a single joint with AVN in BD, even if they are asymptomatic.

It has been suggested that smoking has contributory effect on development of AVN [25]. All patients except for one were smokers. Although there is no study that compares the frequency of AVN between smoker and nonsmoker BD patients, it may be speculated that smoking is a risk factor for AVN in BD. In our study, vascular involvement was dominant involvement in most patients with AVN. This may be due to the effect of vasculitic process on AVN or requirement of high immunosuppressive treatment including CS in these patients. All of BD patients had had immunosuppressive treatment prior to diagnosis of AVN. Immunosuppressive drugs may contribute to AVN by cytotoxic effect on osteoblasts and osteoclasts [26]. But these drugs are also important in the control of active inflammation and they have steroid sparing effects. Thus, the net effect of these drugs on development of AVN is uncertain. In previous reported case, the number of male and female patients was similar. All of patients were male in our study. This may be due to more aggressive course of BD in young male patients with requirement of more intensive treatment, including CS [27].

There is an uncertain relation of antiphospholipid antibodies with development of AVN in SLE. None of our patients had a significantly elevated antiphospholipid antibody level, similar to previous case reports [17, 18]. Despite similar articular involvement with SLE in BD patients in our cohort, the absence of female gender and aCL antibodies suggest different mechanism of action. Similarities were CS use, younger age and articular pattern.

One limitation of this study is that MRI had been performed only in symptomatic patients. When asymptomatic patients on CS treatment are evaluated for development of AVN with MRI, a higher number of BD patients with AVN might be detected.

As a conclusion, although the number of patients is relatively low and to make a clear conclusion, it may be speculated that CS treatment, smoking and vascular type of involvement may predispose to development of AVN in patients with BD. AVN should be considered in BD patients who complaint with joint paint and those receiving CS treatment. Finally, since AVN by itself has significant morbidity and influence treatment decisions it might be better to take

account this complication in damage indices of BD as considered in SLE.

**Author contributions** In accordance with ICMJE criteria, NA designed the study and wrote the initial draft of the manuscript. AT contributed to the design of the study, the collection and interpretation of data, and the assistance of the preparation of the manuscript. All other authors contributed to the data collection and interpretation and revised the manuscript. The literature data were searched and analyzed by all authors. All authors approved the final version to be submitted for publication and agree to be accountable for all aspects of the work.

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## Compliance with ethical standards

**Conflict of interest** Nuh Atas, Berivan Bitik, Ozkan Varan, Hakan Babaoglu, Abdurrahman Tufan, Seminur Haznedaroglu, Berna Goker and Mehmet Akif Ozturk declare that they have no conflicts of interest.

**Ethical approval** Ethical approval was not required for this work because it contains retrospective data of patients and all treatment decisions were made prior to our evaluation.

**Informed consent** Informed consent was obtained from all participants included in the study.

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