Research Article / Araştırma Makalesi

Cardiac Involvement in Patients with Behcet's Disease: A Retrospective, Single-Center Experience

Behçet Hastalarında Kardiyak Tutulum: Retrospektif Tek Merkez Deneyimi

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Abstract: Behcet's disease (BD) is well-known with mucocutaneous involvement, whereas the heart may rarely be involved, predicting morbidity and mortality. In this study, we aimed to reveal the clinical characteristics of cardiac involvement in BD. We retrospectively screened 800 BD patients diagnosed between 2000 and 2021 for cardiac involvement. 14 patients who met these criteria were recruited in this study. Demographic information, clinical features, treatment modalities, and prognosis were evaluated. All patients were male and smokers. The mean age for cardiac involvement was estimated at 32.5 ±7,8 years. Cardiac involvement developed in one-third of the patients before disease diagnosis. Patients were classified into three major groups: 8 of intracardiac thrombosis (ICT), 2 of coronary artery aneurysms, and 4 of myocardial infarction (MI). The majority of ICT was seen in the right ventricle (6 out of 8). In all MI cases, the left main coronary artery was totally occluded. Deep vein thrombosis was seen in 57% of patients. Apart from steroids, cyclophosphamide was the most common preferred agent, used in 9 patients. Azathioprine and interferon use were seen in 4 cases. Warfarin was used in 10 patients and 4 cases received an antithrombotic agent. Mortality was seen in 2 cases due to unknown causes. Cardiac involvement is rare, but a serious manifestation of BD. ICT was the most common type with mostly involved the right heart chambers. Male gender and smoking were found as the most important associated risk factors in this population.
Keywords: Vaccines Behcet's disease, cardiac involvement, intracardiac thrombosis, coronary artery aneurysm, myocardial infarction

Özet: Behçet hastalığının (BH) mukokutanöz tutulumu iyi bilinmektedir, ancak kardiyak tutulum nadirdir ve artmış morbidite ve mortalite ile ilişkilidir. Bu çalışmada, BH'nin kardiyak tutulumunun klinik özelliklerini ortaya koymayı amaçladık. 2000-2021 yılları arasında 800 BH tanılı hastayı kardiyak tutulum açısından retrospektif olarak taradık. Bu kriterleri karşılayan 14 hasta çalışmaya dahil edildi. Demografik bilgiler, klinik özellikler, tedavi yöntemleri ve prognoz değerlendirildi. Hastaların tamamı erkek ve sigara içiyordu. Kardiyak tutulum için ortalama yaş 32,5±7,8 yıl olarak saptandı. Hastaların üçte birinde hastalık tanısı konmadan önce kardiyak tutulum gelişmişti. Hastalar üç ana gruba ayrıldı: 8'i intrakardiyak tromboz (İKT), 2'si koroner arter anevrizması ve 4'ü miyokard infarktüsü (Mİ). İKT'nin çoğunluğu sağ ventrikülde idi (6/8). Mİ olgularının tümünde sol ana koroner arter tamamen tıkanmıştı. Hastaların %57'sinde derin ven trombozu vardı. Steroidler en sık tercih edilen ajandı. 9 hastada Siklofosfamid 4 hastada azatioprin ve interferon kullanılmıştı. 10 hastaya varfarin ve 4'üne antitrombotik ilaç verildiği görüldü. Mortalite izlenen iki olguda ölüm nedeni bilinmiyordu. Kardiyak tutulum nadir olsa da BH'nin ciddi bir tutulum tipidir. Çoğunlukla sağ kalp boşluklarında İKT ile karşımıza çıktığı gözlendi. Erkek cinsiyet ve sigara kullanımı bu popülasyondaki en önemli risk faktörü olarak bulunmuştur.
Anahtar Kelimeler: Behçet hastalığı, kardiyak tutulum, intrakardiyak tromboz, koroner arter anevrizması, miyokardiyal infarktüs.

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1. Introduction

Behcet's disease (BD) is a type of systemic vasculitis manifested by mucocutaneous, eye, neurologic, pulmonary, cardiac, and gastrointestinal involvement [1]. It is prevalent along the 'silk road' and Turkey is one of the places where it is seen most frequently. Cardiovascular involvement is a relatively rare type of presentation for BD, so there is limited data about the clinical spectrum and treatment modalities. While cardiovascular involvement in BD was reported in a range between 7 to 46 %, a cardiac disease without any vascular involvement is relatively uncommon with an estimated prevalence of 1 to 6% in the literature [2-4]. Although rare, cardiac involvement is associated with an increased risk of mortality. As BD can affect any type of vessel as well as the cardiac layers. So, the spectrum can be variable; intracardiac thrombosis (ICT), pericarditis, myocarditis, endocarditis, coronary arteritis, and valvular heart disease [3]. As the mortality and morbidity rates are high in this specific population, even though no agreement on treatment has been available, many experts recommend initiating cyclophosphamide (CYC) in conjunction with high-dose steroids. The role of anticoagulation is still debatable and may complicate high mortality in the presence of a pulmonary artery aneurysm (PAA) [5]. Early detection and appropriate management is may improve the prognosis.

Considering the importance of the life-threatening complications of cardiac involvement in BD, herein we present our experience with the cardiac manifestations of BD in a single center in Turkey. This article was previously presented as a meeting abstract at the 2022 EULAR Conference on May 2022

2. Materials and Metods

2.1. Patient selection

Records of the 800 patients diagnosed with BD based on the International Study Group (ISG) and the International Criteria for Behçet's Disease (ICBD) criteria were retrospectively evaluated [6,7]. BD patients with cardiac involvement are defined as having pericarditis, myocarditis, ICT, myocardial infarction (MI), and coronary artery aneurysm (CAA) [4].

Cardiac involvement diagnosis was based on clinical examination and imaging techniques including transthoracic echocardiography, transesophageal echocardiography, computed tomography angiography, electrocardiography, and coronary angiography. Screening for cardiac involvement was performed in symptomatic patients only. Finally, 14 patients who have diagnosed with BD related cardiac involvement and 14 age and sex matched BD patients with mucocutaneous involvement were included in the study as control group. Demographic information (age, gender, smoking history), clinical manifestations of BD, treatment modalities, and long-term outcome measures were obtained from hospital records. The study was approved by the Local Ethics Committee on 09/11/2021 with decision number 08.

2.2. Statistical analysis

Continuous data are given as mean ± standard deviation, median (Q1-Q3). Categorical data are given as percentage (%). Shapiro Wilk's test was used to investigate the appropriateness of the data to normal distribution. The Mann-Whitney U test was used for the two groups to non-normal distribution. Pearson's chi-square and Fisher Exact chi-square analysis were used in the analysis of the cross tables. IBM SPSS Statistics 21.0 (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.) was used in the implementation of the analyzes. A p value of <0.05 was considered as a criterion for statistical significance.

3. Results

Fourteen BD patients with cardiovascular involvement were included in the study. All patients were male and smokers (Table 1). All patients had a history of oral ulcer (%100), 9 had a genital ulcer (%64), 8 had

osteofolliculitis (%57), 6 had erythema nodosum (%43), 3 had uveitis (%21,4). Pathergy test was positive in 8 patients (%57,1). The mean age at the time of the cardiac event was 32,5 +7,8years. The cardiac event was detected before BD diagnosis in 3 patients, simultaneously with BD in 3 patients, and after BD diagnosis in 8 patients. In those, the mean estimated duration was 4,6 years between cardiac involvement and BD diagnosis. MI developed in 3 patients who developed cardiac involvement before the diagnosis of BD and were referred to the rheumatology department from the cardiology department due to the presence of mucocutaneous findings. The cardiac event was thought to be related to BD since there were mucocutaneous findings before MI and there was no cardiac risk factor other than smoking. ICT, right CAA, and MI were seen in 8 (57%), 2 (14%), and 4 (29%) of patients, respectively. ICT was located in the right heart chambers in all patients (6 in the ventricle and 2 in the atrium). All patients with MI had total occlusion in the left main coronary artery. Deep vein thrombosis (DVT) was seen in 57.1% (n: 8) of all cases; 3 simultaneously, 2 before, and 3 after cardiac involvement. Of the 8 patients with DVT, 3 had ICT concurrently.

Among the ICT population, a combination of cyclophosphamide (CYC) and corticosteroids was preferred in 7 cases, whereas corticosteroid monotherapy was used in one patient who had been followed by another clinic. Three patients with MI received azathioprine (AZA) and corticosteroid, while one case was followed only by an anti-thrombotic agent without immunosuppressive treatment after coronary stent placement. All CAA patients were treated with CYC and steroids. AZA was administered as maintenance in all patients receiving CYC. Seven patients with ICT, 2 with MI, and 1 with CAA received warfarin. MI developed in one patient while receiving AZA treatment. Furthermore, ICT developed in two patients receiving colchicine for mucocutaneous lesions. Pulmonary involvement developed in 4 patients (3 with pulmonary thrombosis, 1 with PAA), all in those with ICT. Complete disappearance of thrombus on echocardiography was observed in duration between 3 to 26 months (mean 9,8 months) in all patients with ICT after treatment. 9 patients are still on follow-up, 3 were lost in follow up and 2 died due to other reasons (Table 2). Clinical features of BD patients with cardiac involvement were compared with 14 age and sex-matched BD patients with mucocutaneous involvement. BD patients with and without cardiac involvement did not show differences in terms of genital ulcer, osteofolliculitis, erythema nodosum, HLA B5 positivity and duration of disease. Pathergy test was performed in 8 of the BD patients with cardiac involvement and all were positive, whereas it was performed in 10 of the BD patients with mucocutaneous involvement and 4 were positive (p:0.013).

Table 1. Demographic and clinical characteristics of 14 BD patients with cardiac involvement

Demographic features	**n (%)**
Age, years (mean ± SD)	32.5 ± 7.8
Diagnosis age, years (mean ± SD)	30 ± 7
Gender, male	14 (100)
Smoking history	14 (100)
Clinical features	**n (%)**
Oral ulcer	14 (100)
Genital ulcer	9 (64.2)
Osteofolliculitis	8 (57.1)
Erythema nodosum	6 (43)
Uveitis	3 (21.4)
Pathergy positivity	8 (57.1)
Vascular involvement	11 (78.5)
- DVT	8 (57.1)

- Pulmonary involvement	4 (28.5)
- Pulmonary artery aneurysm	1 (7.1)
CNS involvement	2 (14.3)
GIS involvement	3 (21.4)

DVT: deep vein thrombosis, CNS: central nervous system, GIS: gastrointestinal system, N: number, SD: standart deviation, BD: Behcet's disease

Table 2. Types of cardiac involvement, treatment choices, and prognosis

Type of cardiac involvement	**n (%)**
Intracardiac thrombosis	8 (57.1)
RV	6
RA	2
Coronary artery aneurysm	2 (14.3)
Myocardial infarction	4 (28.6)
Treatment	**n (%)**
Steroid	14 (100)
Cyclophosphamide	9 (64,2)
Azathioprine	3 (21.-.4)
Anticoagulation	10 (71.4)
Antithrombotic	4 (28.6)
Prognosis	**n (%)**
On follow-up	9 (64.2)
Lost follow up	3 (21.4)
Mortality	2 (14.3)

RV: right ventricle, RA: right atrium,

Table 3. Comparison of clinical characteristics of BD patients with and without cardiac (mucocutaneous) involvement

	BD patients with isolated mucocutaneous involvement n (%)	**BD patients with cardiac involvement n (%)**	**P value**
Genital ulcer,	11 (78.6)	9 (64.3)	0.678**
Osteofolliculitis	13 (92.9)	8 (57.1)	0.077**
Erythema nodosum	10 (71.4)	6 (42.9)	0.127*
Pathergy positivity	4 (40.0)	8 (100.0)	**0.013****
HLA-B51 positivity	4 (50.0)	1 (100.0)	1.000**
Age (mean ± SD)	42.14 ± 13.13	47.14 ± 10.44	0.401***
Disease duration, years (mean ± SD)	13.21 ± 9.48	16.29 ± 6.99	0.178***

N: number, SD: standart deviation, BD: Behcet's disease
**Pearson Chi-Square Test*
***Fisher Exact Test*
**** Mann Whitney U Test*

4. Discussion

In the current study, there were 14 BD patients with cardiac involvement out of 800 BD patients (1,75%). All patients were male and smokers. ICT was the most common cardiac manifestation. Despite its reported low prevalence rates (1-6%) in the literature, cardiac involvement might be observed as high as 16,5% according to post-mortem studies in BD patients [2-4,8]. In the current study, the frequency of cardiac involvement was 1,75%, consistent with previously published data.

It is well known that major organ involvement such as eye, pulmonary, and central nervous system predominantly affects the male population in BD [9]. Similarly, all patients with cardiac involvement in the study group were male. Several literature data have shown that cardiac involvement is associated with DVT, PAA, and thrombosis of superior and/or inferior caval veins [3,4,9]. Accordingly, vascular involvement was present in 78,5% of our cases, with DVT being the most common (57,1%). Three of the patients had DVT concurrently with ICT. Even though

thromboembolism is not an expected complication in BD, similar data was observed in BD patients with pulmonary involvement [10]. Of course, this mustn't make us think about embolism but have to be vigilant about another thrombosis meanwhile. So, BD patients with DVT must be evaluated for thrombosis located on another side.

BD may involve the heart with variable spectrums. Our study findings have shown that cardiac involvement can be classified into 3 major groups: ICT, MI, and CAA. According to the literature, pericarditis is the most common type of cardiac involvement in BD [3,4,11]. None of the patients had pericarditis among the study population. This finding might be explained by several reasons: not performing routine echocardiography in asymptomatic patients, the possible effect of colchicine in masking pericarditis symptoms, and the asymptomatic course in some patients. Besides, endocardial involvement, aortic and mitral valve insufficiencies are other reported types of cardiac manifestations [3,12]. No endocardial involvement was seen in our study population. In our country, rheumatic valve disease is still the leading cause of cardiac valve disease in adult population, especially the elderly. Of note, we excluded the cardiac valve pathologies because it would be difficult and very speculative to attribute them to BD.

ICT in BD is a rare but serious involvement. In large series, its prevalence has been estimated to be approximately 1% among all BD patients [3,4,13]. Also, it may sometimes be the presenting or preceding manifestation of the disease [13]. In our study, the prevalence was found similar to the literature and ICT was the presenting feature in 3 patients. Almost always ICT originated in the right ventricle whereas left-sided involvement might rarely occur [3,13,14]. Similar to the literature, all ICT cases were seen in the right heart chambers in the study population. From this point of view, a thrombus formation (sometimes it is misdiagnosed as a mass) in the right ventricle (Figure 1, 2) when presenting in a young male should raise suspicion of BD diagnosis. Due to the increased co-existence between ICT and pulmonary arterial involvement in many observational studies, it has been hypothesized that thrombus formation in the right heart chambers may be the main source of in-situ thrombosis of the pulmonary artery [9,15]. However, it was unable to prove this in the post-mortem series [8]. Pulmonary arterial involvement was seen in 4 out of 8 ICT patients in the study. Thus, in case of a thrombus formation in the right heart chambers of a young male, an extensive radiologic examination should be performed whether pulmonary involvement is accompanying.

Coronary artery involvement in BD may present with clinical manifestations of silent ischemia, stable angina pectoris, or myocardial infarction [16-18], typically in the form of stenosis, occlusion, or aneurysm formation [19]. The prevalence of coronary artery disease (CAD) in BD has been previously reported between 1 to 4% in the literature [3,11,19]. We have found the cumulative frequency of MI and CAA as 0,75%, with all CAA cases involving the right system. The slightly low rate of CAD may be the result of the relatively small number of the study group.

Due to its rarity and lack of prospective evidence, treatment is generally based on experts' recommendations from a series of vascular involvement. Management consists of steroids in conjunction with CYC, AZA, and infliximab. All patients with CAA received CYC, followed by AZA maintenance in terms of a life-threatening complication. Anticoagulation is still an area of debate in BD. Although anticoagulation therapy alone has not been shown to prevent the development of venous thrombosis [20], Geri et al, revealed the benefit of anticoagulation in patients with **ICT** [3]. Furthermore, in a retrospective study, adding immunosuppression decreased the relapse of thrombosis fourfold in these patients [21]. In light of this information, a combination of immunosuppression with anticoagulation in the case of BD patients with cardiac thrombosis is generally recommended due to relatively increased complete remission rates that have been shown in previous observational studies. In our study population, 13 out of 14 cases successfully received either

anticoagulation or antithrombotic (10 and 4), without any complications and the mortality rate in our group was lower than in the literature. This may be explained by the treatment approach including combination regimens.

Clinical characteristics of BD patients with cardiac involvement were compared with patients with mucocutaneous involvement. There was no difference in terms of genital ulcer, osteofolliculitis, erythema nodosum development, HLA B5 positivity, age, and duration of disease. But the pathergy test was positive in all applicants. Based on the literature, this may be explained in two ways;1. Assar et al reported that pathergy was positive mostly in males, whereas all our patients were male, 2. Pathergy positivity is more common in BD patients with vascular involvement [22,23].

Our study has some limitations. Retrospective design causing loss of data during follow-up and the small number of patients recruited in this study are major limitations. The potential impact of risk factors for cardiovascular disease other than smoking could not be assessed. As above-mentioned, extensive radiologic examination performed especially in the presence of clinical symptoms might have underestimated the detection of pericarditis and other types of cardiac involvement.

5. Conclusion

Cardiac involvement is an exceptionally rare clinical condition in BD patients. Young age at onset, male gender, smoking, and DVT history seem to be important risk factors. Clinicians must be aware of thrombosis located elsewhere in BD patients with DVT. Of note, pulmonary vasculature should be also evaluated for concurrent involvement, particularly in the presence of ICT. Although no screening protocols are currently available, patients with high-risk factors should be carefully investigated to provide a better outcome over the long term. As Behcet's-related cardiac disease is treatable, close cardiac monitoring of Behcet's patients has extreme importance. Studies about routine monitoring for cardiac involvement including all BD patients may give more data about this rare situation.

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Ethic

Ethics Committee Approval: The study was approved by Eskisehir Osmangazi University Noninterventional Clinical Research (Decision no:8, Date: 09.11.2021)
Informed Consent: Written informed consent was obtained from each participants.
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