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ORIGINAL ARTICLE

Coronary involvement in patients with Behçet's disease

Hua Chen[1,2] · Yuehua Zhang[1,2,3] · Chaoran Li[1,2] · Wei Wu[4] · Jinjing Liu[1,2] · Fengchun Zhang[1,2] · Wenjie Zheng[1,2]

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Abstract

Objectives To investigate the clinical features and potential risk factors of coronary involvement in Behçet's disease (BD).

Method In this case-control study, we retrospectively reviewed medical records of BD patients admitted to our institute from 2000 to 2016. Coronary involvement was documented by coronary angiography and (or) computed tomography angiography. We analyzed the demographic, clinical, and laboratory data and compared with age- and gender-matched BD patients without coronary involvement.

Results Among 476 BD patients (296 males) enrolled, 19 (4.0%) patients (17 males) were diagnosed with coronary involvement. The median duration from onset of BD to coronary involvement was 2.8 years. Coronary stenosis, aneurysm, and occlusion were presented in 13, 9, and 3 patients, respectively. Multiple coronary artery stenoses and aneurysms were observed in 9 and 3 patients, respectively. Smoking (36.8%) was the major traditional risk factors. Male gender (89.5% vs 61.1%, $p = 0.01$), skin lesions (78.9% vs 55.3%, $p = 0.08$), pathergy reactions (36.8% vs 10.5%, $p = 0.01$), extra-cardiac vasculitis (36.8% vs 6.6% $p < 0.01$), elevated ESR (57.9% vs 34.2%, $p = 0.01$), and elevated CRP (63.2% vs 42.1%, $p < 0.01$) were more common in BD patients with coronary involvement comparing with those without coronary involvement. Multivariate analysis confirmed pathergy reaction (OR = 3.81, 95% CI 1.08–13.47) was the independent risk factor.

Conclusions Coronary involvement in BD patients is rare and male-predominant and is characterized by the aneurysm and multivessel involvement. Elevated ESR and CRP are frequent, and the pathergy reaction is the independent risk factor.

Key Points

- *Coronary involvement in BD patients is rare and male-predominant.*
- *Pathergy reaction is the risk factor for coronary involvement in BD patients.*

Keywords Behçet's disease · Cardiovascular diseases · Risk factors · Vasculitis

Hua Chen and Yuehua Zhang contributed equally to this work.

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✉ Wenjie Zheng
wenjzheng@gmail.com

[1] Department of Rheumatology and Clinical Immunology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, 1 Shuaifuyuan, Dongcheng District, Beijing 100730, China

[2] Key Laboratory of Rheumatology & Clinical Immunology, Ministry of Education, Beijing, China

[3] Department of Oncology and Immunology, The fourth hospital of Hebei Medical University, Hebei 050000, China

[4] Department of Cardiology, Peking Union Medical College Hospital, Beijing, China

Introduction

Behçet's disease (BD) is a chronic systemic inflammatory condition characterized by recurrent oral and genital ulcerations [1]. Vascular manifestation is the hallmark of BD, which potentially affects the large-, medium-, and small-sized arteries and veins [2]. Coronary involvement, i.e., coronary artery involvement, is a rare and potentially fatal complication of BD [3], which is presented as angina pectoris, arrhythmia, acute myocardial infarction or even cardiac death. To date, only limited cases of BD patients with coronary involvement are reported [4–8]. Given the life-threatening risk of coronary involvement, a well understanding of the clinical characteristics and predictive factors of coronary involvement in BD were warranted.

To identify the clinical features and potential risk factors of coronary involvement in BD, we retrospectively analyzed the hospitalized BD patients and identified the patients with

coronary involvement. We summarized the clinical features of coronary involvement as well as the clinical characteristics of BD and further explored the potential risk factors for coronary involvement in BD patients.

Materials and methods

Patients

In this case-control study, we retrospectively enrolled the BD patients admitted to Peking Union Medical College Hospital from 2000 to 2016. The inclusion criteria were fulfilled 1990 International Study Group BD criteria [9] or the International Criteria for BD (ICBD) [10], coronary involvement documented by coronary angiography, and computed tomography angiography. The exclusion criteria were atherosclerotic coronary artery disease. The coronary involvement was screened in patients with ischemic cardiomyopathy symptoms and (or) ischemic electrocardiography (ECG) changes and was confirmed by coronary angiography ($n = 12$, $\kappa = 1.00$) and (or) computed tomography angiography ($n = 10$, $\kappa = 0.87$) findings, which was defined as aneurysm (luminal diameter two or more times wider than that of adjacent normal segments), stenosis (> 50% without evidence of atherosclerosis), and occlusion [11]. The diagnosis of coronary involvement was established by the consensus of two independent experienced cardiologists who were blind to patients' BD condition. Coronary involvements caused by BD were determined by the following imaging criteria: (1) angiographic coronary aneurysm; (2) atypical lesion sites, e.g., orifice of left main or right coronary artery; (3) supplemental intracoronary imaging evidence such as intravascular ultrasound or optical coherence tomography. We enrolled all the patients with coronary involvement. For the control group, the age- and sex-matched BD patients without ischemic cardiomyopathy symptoms and abnormal ECG were randomly selected at 1:4 ratio. The study was reviewed and approved by the institutional ethics review board of Peking Union Medical College Hospital per the Declaration of Helsinki. Given that the study was based on the review of medical records, written informed consent was waived.

Data extraction

Clinical data, including demographics, traditional cardiovascular risk factors, BD manifestations, cardiac symptoms, coronary and peripheral vascular involvements, laboratory examinations, treatment, and outcome, were retrospectively collected from the medical records.

Statistical analysis

All descriptive data are expressed as mean ± SD, median (range), or frequencies (%). Normally and non-normally distributed quantitative variables were compared using two-sample t test and Mann-Whitney U test, respectively. Categorical variables were compared using Fisher's exact test. Univariate logistic regression analysis was used to evaluate candidate predictors of coronary involvement, and the variables with p value < 0.1 were selected in the multivariate analysis. A two-sided p value < 0.05 was considered statistically significant. The data were processed using SPSS version 22.0 software (IBM Inc., Armonk, USA).

Based on our preliminary observations in BD patients, the pathergy reaction was observed in approximately 40% of patients with coronary involvement and in 10% of patients without coronary involvement. To provide the two-sided statistical analyses with sufficient statistical power of 0.80 ($\beta = 0.20$ and $\alpha = 0.05$), a total of 17 patients with coronary involvement and 68 patients without coronary involvement were required for the study. The sample size was calculated by PASS version 11 (NCSS, Kaysville, USA).

Results

Demographics and cardiac manifestations

In total, 476 BD patients (296 males and 180 females) were enrolled. Coronary involvement was documented in 19 (4.0%) patients (Table 1). The male percentage in patients with coronary involvement was significantly higher than those without coronary involvement (89.5%, $n = 17$ vs 61.1%, $n = 279$, $p = 0.01$). The mean age of the patients with coronary involvement and those without coronary involvement was 34.0 and 36.5 years ($p = 0.40$), respectively. Angina pectoris (42.1%) and acute myocardial infarction (42.1%) were the most common cardiac symptoms, followed by ventricular arrhythmia in one patient (5.3%). Three patients (15.8%) were asymptomatic (Table 2) but were presented with ischemic ECG changes. The cardiac manifestations were developed at and after the onset of BD in 2 and 17 patients, respectively, with a median interval of 2.8 (range, 0–20.3) years.

Traditional cardiovascular risk factors

Smoking (36.8%) was the most prevalent risk factor in patients with coronary involvement, followed by hypertension (15.8%) and diabetes mellitus (10.5%). Additionally, obesity (5.3%) and alcohol abuse (5.3%) were rarely presented, and no hyperlipidemia was documented (Table 2).

Table 1 Demographic, baseline, and laboratory features of BD patients with or without coronary artery involvement

	Coronary involvement ($n = 19$)	No coronary involvement ($n = 76$)	p value
Gender (M/F)	17/2	68/8	1.00 [a]
Age (yr, mean ± SD, median)	34.0 ± 12.9 (32.0)	35.5 ± 10.3 (33.5)	0.16 [a]
BD manifestations			
Oral ulceration (n, %)	19 (100%)	76 (100%)	1.00
Skin lesions (n, %) [b]	15 (78.9%)	42 (55.3%)	0.07
Genital ulceration (n, %)	12 (63.2%)	47 (61.8%)	1.00
Pathergy reaction (n, %)	7 (36.8%)	8 (10.5%)	0.01
Extra-cardiac vasculitis (n, %)	7 (36.8%)	5 (6.6%)	< 0.01
Uveitis (n, %)	3 (15.8%)	20 (26.3%)	0.55
Arthritis (n, %)	3 (15.8%)	8 (10.5%)	0.45
Gastrointestinal involvement (n, %)	2 (10.5%)	15 (19.7%)	0.51
Neuropathy (n, %)	1 (5.3%)	0 (0%)	0.20
Laboratory			
Elevated ESR (%) [c]	11 (57.9%)	26 (34.2%)	0.01
Elevated CRP (%) [d]	12 (63.2%)	32 (42.1%)	< 0.01
AECA positive (n, %)	2/15 (13.3%)	15/53 (28.3%)	0.32
Cardiovascular risk factors (n, %)			
Smoking	7 (36.8%)	17 (22.4%)	0.24
Hypertension	3 (15.8%)	4 (5.3%)	0.14
Diabetes mellitus	2 (10.5%)	3 (3.9%)	0.26
Hyperlipidemia	0 (0%)	3 (3.9%)	1.00
Obesity	1 (5.3%)	9 (11.8%)	0.68
Alcohol abuse	1 (5.3%)	2 (2.6%)	0.50

AECA, anti-endothelial cell antibodies

[a] Age- and sex-matched patients

[b] Skin lesions include pseudofolliculitis ($n = 6$), erythema nodosum ($n = 5$), and pustule ($n = 4$)

[c] Defined as > 15 (male) or 20 (female) mm/h

[d] Defined as > 8 mg/L.

Coronary involvement

Coronary angiography and computed tomography angiography were performed in 12 and 9 patients, respectively. Left anterior descending artery ($n = 13$) and right coronary artery ($n = 10$) were the most commonly affected coronary arteries, followed by left circumflex artery ($n = 9$) and left main coronary artery ($n = 2$). Coronary stenosis was documented in 13 (68.4%) patients, and multiple coronary stenoses (47.4%) were more common than single coronary stenosis (21.1%). Coronary aneurysm was observed in 9 (47.4%) patients (Fig. 1b, Supplement Video 1), including 3 (15.8%) patients with multiple aneurysms. Furthermore, coronary artery occlusion was presented in 3 (15.8%) patients (Fig. 1a, Supplement Video 2). Additionally, extra-cardiac arterial ($n = 7$) and venous lesions ($n = 2$) were presented in 7 (36.8%) patients (Table 2).

BD manifestations

Oral ulceration was presented in all patients with coronary involvement, followed by skin lesions (78.5%) including pseudofolliculitis (31.6%), erythema nodosum (26.3%), and pustule (21.1%). Genital ulceration (63.2%) and pathergy reaction (36.8%) were frequently presented, but uveitis (15.8%), arthritis (15.8%), gastrointestinal involvement (10.5%), and neuropathy (5.3%) were uncommonly observed (Table 1). Additionally, fever, fatigue, and weight loss were observed in 3 (15.8%), 6 (31.6%), and 2 (10.5%), respectively.

Laboratory examinations

The median erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) levels in patients with coronary involvement were 28.0 mm/h and 18.0 mg/L, respectively. Elevated erythrocyte sedimentation rate (ESR), defined as >

Table 2 Clinical and radiological characteristics of coronary artery involvement in BD

	Coronary involvement ($n = 19$)
Cardiac manifestations (n, %)	
Angina pectoris	8 (42.1%)
Acute myocardial infarction	8 (42.1%)
Arrhythmias[a]	1 (5.3%)
Asymptomatic	3 (15.8%)
Coronary artery involvement (n, %)	
Left anterior descending artery	13 (68.4%)
Right coronary artery	10 (53.2%)
Left circumflex artery	9 (47.4%)
Others[b]	2 (10.5%)
Aneurysm (n, mean ± SD)	9 (47.4%, 1.4 ± 0.7)
Multiple aneurysm[c]	3 (15.8%)
Stenosis (n, mean ± SD)	13 (68.4%, 2.1 ± 0.9)
Multiple stenosis[c]	9 (47.4%)
Occlusion	3 (15.8%)
Extra-cardiac vascular involvement (n, %)	7 (36.8%)
Arterial	7 (36.8%)
Venous	2 (10.5%)

[a] Ventricular tachycardia

[b] Left main coronary artery ($n = 2$)

[c] Two to three lesions

15 (male) or 20 (female) mm/h, was observed in 57.9% of patients with coronary involvement. Elevated C-reactive protein (CRP), defined as > 8 mg/L, was observed in 63.2% of patients with coronary involvement. Anti-endothelial cell antibodies were positive in 2 out of 15 patients (13.3%), and antinuclear antibodies were all negative (Table 1).

Treatment and outcomes

Given that vital vessels including coronary arteries were affected by BD as well as the frequently elevated ESR and CRP, the patients were treated aggressively. All patients received a mean initial dose of 0.93 mg/kg d prednisone or equivalent glucocorticoid, and one patient also received methylprednisolone pulse therapy. All patients received immunosuppressants, including 8 (42.1%) patients who received a combination of two to three immunosuppressants. All patients received individualized cardiovascular treatment, including aspirin, heparin, and warfarin in patients with high thrombosis risk, beta blockers, and angiotensin-converting enzyme inhibitors in patients with myocardial infarction. Besides, percutaneous coronary revascularization was performed in 3 (15.8%) patients (Table 3). During a median follow-up period of 15 months, 15 (78.9%) patients achieved clinical remission, which was defined as the absence of cardiac and BD symptoms, as well as the normalized ESR and CRP. However, the cardiac condition exacerbated in 2 (10.5%) patients, and cardiac death was documented in one patient with heart failure and one patient with sudden cardiac death (Table 3).

Risk factors for coronary involvement in BD patients

We randomly selected 76 age- and sex-matched BD patients without ischemic cardiomyopathy symptoms and abnormal ECG as the control. We observed no statistical difference in the traditional cardiovascular risk factors between the groups.

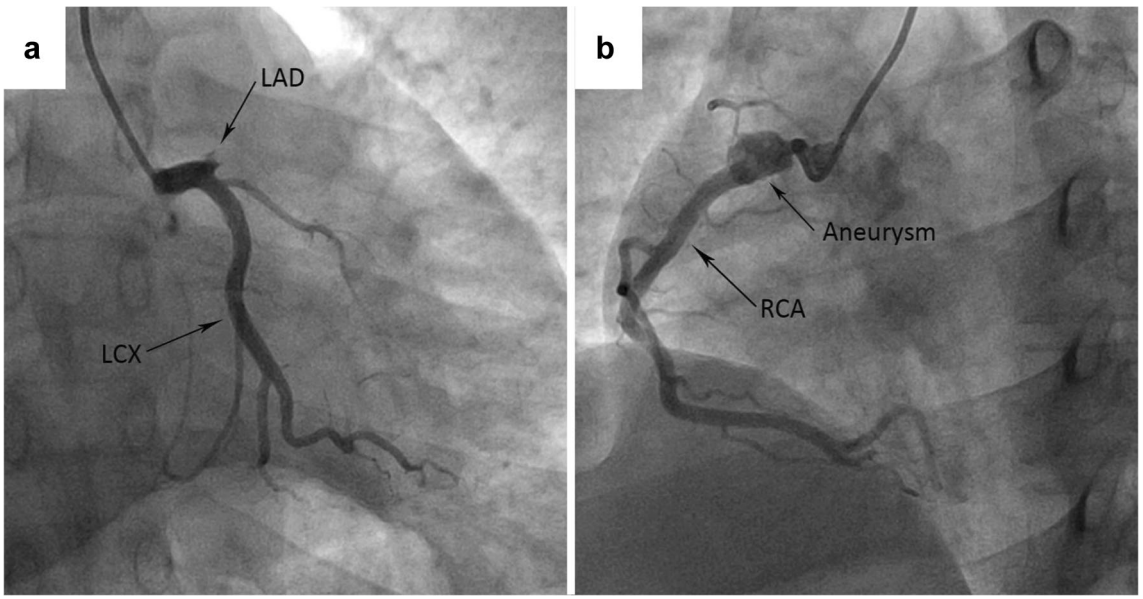

Fig. 1 Angiography of the coronary involvement of a patient with BD. **a** An occlusion (arrow) at the proximal segment of the left anterior descending (LAD) artery, and the normal left circumflex (LCX) artery. **b** An aneurysm (arrow) at the proximal segment of right coronary artery (RCA)

Table 3 Treatment and outcome of BD patients with coronary artery involvements

	Coronary involvement ($n = 19$)
Glucocorticoid	
Initial dose (mg/kg d, mean ± SD) [a]	0.93 ± 0.47
Maintenance dose (mg/kg d, mean ± SD)	0.25 ± 0.18
Immunosuppressant (*n*, %)	
Cyclophosphamide	16 (84.2%)
Thalidomide	3 (15.8%)
Azathioprine	2 (10.5%)
Methotrexate	2 (10.5%)
Others[b]	4 (21.1%)
Combination therapy	8 (42.1%)
Percutaneous coronary revascularization (*n*, %)	3 (15.8%)
Follow-up (month, mean ± SD, median)	16.5 ± 13.5 (15.0)
Outcome (*n*, %)	
Remission	15 (78.9%)
Exacerbation	2 (10.5%)
Death	2 (10.5%)

[a] Dose is defined as prednisone or equivalent. One patient receives methylprednisolone pulse therapy

[b] Cyclosporine, mycophenolate, sulfasalazine, and hydroxychloroquine are used in one patient, respectively

However, we identified that skin lesions (78.9% vs 55.3%, $p = 0.08$), pathergy reaction (36.8% vs 10.5%, $p = 0.01$), extra-cardiac vasculitis (36.8% vs 6.6% $p < 0.01$), elevated ESR (57.9% vs 32.2%, $p = 0.01$), and elevated CRP (63.2% vs 42.1%, $p < 0.01$) were the candidate risk factors (Table 1). We focused on non-vascular factors, and univariate logistic regression analysis revealed that pathergy reaction (OR = 4.96, 95% CI 1.52–16.23) and elevated CRP (OR = 3.30, 95% CI 1.06–10.30) were the potential risk factors (Table 4). Finally, multivariate logistic regression analysis confirmed that pathergy reaction (OR = 3.81, 95% CI 1.08–13.47) was the independent risk factors for coronary involvement (Table 4).

Discussion

Cardiac involvements of coronary arteries, conduction system, endocardium, and myocardium, are presented in 7–46% of BD patients [12]. A national-wide study reveals that the prevalence of coronary artery disease (CAD) in BD patients is 12.1% [13], but Ozeren et al. report that the prevalence of coronary involvement in BD is less than 0.5% [14], and Bletry et al. report that the prevalence of myocardial infarct is 2.0% [4]. Additionally, the incidence of coronary aneurysm, the primary coronary lesion in BD patients, is 1.5–5% [15]. Similarly, we showed that the incidence of coronary involvement in BD patients was 4.0%. Notably, a small portion of patients with coronary involvement remain asymptomatic, which might contribute to an underestimation of the prevalence in symptom-driven studies. Together, coronary involvement is a rare presentation of BD.

Most of BD patients (89.5%) with coronary involvement were male (M:F = 8.5:1), which is much more prevalent than general BD patients (M:F = 1.3:1) or patients without coronary involvement (M:F = 1.6:1) [16]. The onset age of cardiac ischemia symptoms in BD patients with coronary involvement was much younger than those in general patients with coronary artery disease, which suggested that coronary involvement in BD was non-atherosclerotic.

Traditional cardiovascular risk factors, including smoking, hypertension, hyperlipidemia, diabetes, obesity, and alcohol abuse, are potentially contributed to coronary involvement in BD patients [13]. Pandey et al. report that hypertension and hyperlipidemia are the predictors of CAD in BD patients [13]. However, we observed smoking, but not hypertension or hyperlipidemia was commonly presented. Furthermore, the prevalence of traditional cardiovascular risk factors was comparable between patients with coronary involvement and patients without coronary involvement. The difference in ethics and diets might explain the discrepancy. Importantly, our data suggested that the mechanism of coronary involvement in BD patients was different from those in the general population, and atherosclerosis was probably not the primary cause.

Table 4 Risk factors associated with coronary involvement in BD patients

	Univariate analysis		Multivariate analysis	
	OR (95% CI)	*p* value	OR (95% CI)	*p* value
Pathergy reaction	4.96 (1.52–16.23)	0.01	3.81 (1.08–13.47)	0.04
Skin lesions	3.04 (0.92–10.00)	0.07	2.11 (0.60–7.43)	0.25
Elevated ESR[a]	2.64 (0.95–7.38)	0.06	2.23 (0.55–8.99)	0.26
Elevated CRP[b]	3.30 (1.06–10.30)	0.04	0.98 (0.23–4.11)	0.97

All variables with p value < 0.1 in univariate analysis were enrolled in the multivariate analysis. *OR*, odds ratio

[a] Defined as > 15 (male) or 20 (female) mm/h

[b] Defined as > 8 mg/L.

Coronary involvement in BD has distinct characteristics. We observed that coronary aneurysm was the most common lesions (47.4%), which is reported more frequently than coronary stenosis in BD but is rarely reported in atherosclerotic CAD (0.3–5.3%) [17, 18]. Furthermore, multiple coronary stenoses and aneurysms (63.2%) were frequently observed in BD patients, which were more common than those in atherosclerotic CAD (57%) [19–21]. Additionally, extra-cardiac arterial and venous lesions were also frequently presented (36.8%) in our study and other studies [5, 7]. Together, the coexistence of coronary and extra-cardiac vascular lesions implicated a shared disease mechanism among the vascular lesions, which is presumably caused by inflammatory cell-mediated vascular wall destruction and subsequent weakening.

Surprisingly, pathergy reaction was the independent risk factor for coronary involvement. Pathergy reaction is a hallmark of BD [22] and a key element of the classification criteria [9, 10]. Histologically, pathergy reaction is characterized by intense infiltration of mononuclear cells around dermal vessels and high-level expression of proinflammatory cytokines, chemokines, and adhesion molecules [23]. Thus, a positive pathergy reaction is a sign of active BD. Furthermore, elevated inflammatory markers such as ESR and CRP were also frequently observed in patients with coronary involvement. Given that the vascular lesions of BD are featured as infiltration of the inflammatory cell in the vascular wall, positive pathergy reaction might suggest an intense inflammation in the vascular wall of coronaries and the subsequent destruction of the coronaries.

Our study has several limitations. First, the control group consisted of patients without cardiac symptoms or abnormal ECG, which might be confounded with asymptomatic patients with coronary involvement. However, given the low incidence (4.0%) of coronary involvement in BD and low frequency (15.8%) of asymptomatic coronary involvement, the estimated misclassification of the patients with coronary involvement in the control group ($n = 76$) is less than one patient. Second, although we reported the largest cohort of BD patients with coronary involvement to date, we identify only one prediction factor due to the limited number of cases. Third, all patients were enrolled from a national referral center, which might induce potential selection bias. However, given the low incidence of coronary involvement in BD, it is impracticable to enroll sufficient cases in general medical centers. A large prospective multi-center case-control study is warranted to address these limitations.

In summary, coronary involvement in BD patients is rare, male-predominant, and early-onset. Coronary aneurysm and multivessel coronary involvement, as well as extra-cardiac vascular lesions, are the hallmarks. Most of the traditional cardiovascular risk factors except smoking are absent. Elevated ESR and CRP are frequent, and the pathergy reaction is the independent risk factor.

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Compliance with ethical standards

The study was reviewed and approved by the institutional ethics review board of Peking Union Medical College Hospital per the Declaration of Helsinki. Given that the study was based on the review of medical records, written informed consent was waived.

Disclosures None.

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