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Literature Review

Acute coronary syndrome in Behcet's syndrome: A systematic review

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Abstract

Behcet syndrome is a rare vasculitis that affects both arteries and veins. Vasculo-Bechet Syndrome (VBS) is seen predominantly in men. Genetic predisposition and immune dysregulation leading to inflammation, endothelial damage, and impaired fibrinolysis contribute to its pathogenesis. Isolated case reports of Behcet syndrome (BS) with associated acute coronary syndrome (ACS) have been reported in the past. In this study, we present the first systematic review of such cases. A systematic search was conducted using Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL, and Web of Science databases from 1980-2018 to identify case reports of myocardial infarction associated with BS. Cases that fulfilled the criteria for BS were selected for analysis. Demographic data, electrocardiography, echocardiography, angiography findings, and management were analyzed when available. We identified 62 case reports. Most subjects were men with a mean age of 37 years. Twenty-one percent were smokers, but other traditional cardiovascular risk factors were less common. Myocardial infarction was confirmed in half of the cases with findings on electrocardiogram (ECG). Echocardiogram revealed wall motion abnormality in 76% of patients, and angiography showed double-vessel disease in more than half of the cases. Mortality was reported in 1.6% of the cases. This systematic review shows that ACS in BS affects young males with low prevalence of coronary artery disease risk factors. Chest pain is the most common presenting feature and ST-segment elevation myocardial infarction (STEMI) was the most common ECG finding. Immunotherapy may be helpful to prevent future ACS in these patients.

Keywords: Behcet syndrome, Behcet disease, acute myocardial infarction, myocardial infarction

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Introduction

Behcet's syndrome (BS) is a rare vasculitis that typically causes relapsing and remitting recurrent oral aphthous ulcers, genital ulcers, and ocular lesions (1). It was first described by Hippocrates but the disease is named after the Turkish dermatologist who described this condition in the early 20th century (2). The diagnosis of BS remains clinical since there are no reliable biomarkers for the detection of this disorder. Several diagnostic and classification criteria are available (3).

Vascular manifestations of BS were described as early as 1946, and these usually affect young men. Vasculo-Behcet's syndrome (VBS) may involve both arteries and veins (4-6). In one large case series, vascular involvement was present in 49% of subjects (6). Venous involvement was more common than arterial lesions with venous disease in 70.6%, arterial lesions in 54.9%, and both arterial and venous lesions in 25.5% (6). Vascular involvement is associated with increased risk of mortality in patients with BS, especially in men, with higher mortality early in the course of disease. The 5-year survival of patients with BS and cardiac involvement is 83.6% compared with 95.8% in those without cardiac involvement (7).

The etiology of BS is unknown but immune dysregulation, genetics, inflammation, endothelial damage/dysfunction, and impaired fibrinolysis contribute to the pathogenesis of VBS (8). HLA-B*51 is the most well-established genetic marker for BS, (9) although other non-HLA genes such as the MEFV gene and familial Mediterranean fever are also associated with this disorder. Pathogenesis is complex with activation of T-lymphocytes, including T helper 17 cells, immune complex formation, neutrophil activation, and increased inflammatory cytokines. The histologic findings include perivasculitis with neutrophil infiltration, fibrinoid necrosis, and endothelial swelling (10). The arterial lesions in BS may be occlusive or aneurysmal (8).

A time interval of 3-16 years has been observed between onset of BS and arterial manifestations (11). Corticosteroids and immunosuppressive therapy are known to prevent relapse and aneurysm formation at the site of arterial anastomosis (12). The European League against Rheumatism 2018 recommendations for management of Behcet's syndrome include cyclophosphamide and corticosteroids for aortic and peripheral artery aneurysms (13). A combination of immunosuppressants, corticosteroids, and anticoagulants was shown to be effective in a large retrospective study of VBS (14). Use of biologic agents with specific immune targets is reported in case reports, but there are no controlled data on the use of these agents in patients with BS and coronary artery involvement (15).

Vascular-BS involving the heart carries high risk for morbidity and mortality including acute coronary syndrome (ACS) (5). We decided to perform a systematic review of these cases to understand the characteristics of patients with BS who present with ACS with the aim of early recognition and treatment of this serious complication.

Methods

On January 2, 2018, a systematic search was conducted using Pubmed, Google Scholar, CINAHL, Cochrane CENTRAL, and Web of Science databases from 1980-2018 for case reports of patients with acute myocardial infarction and BS. We used the keywords "Behcet's disease, Behcet's syndrome, acute myocardial infarction, myocardial infarction, non-ST-segment elevation myocardial infarction (NSTEMI), ST-segment elevation myocardial infarction (STEMI), and coronary artery" to identify case reports of myocardial infarction associated with BS. The reference list of each publication was reviewed for potential additional case reports. All identified cases were reviewed in detail. The cases were reviewed by P.T.K, P.S., and A.J. for relevancy. Data reviewed included demographic data, chief complaint, vital signs, BS manifestations, CV risk factors, electrocardiography (ECG) findings, troponin levels, associated triggering activity, transthoracic echocardiography, angiography, management acute coronary syndrome, and management of BS when available. All cases that identified the clinical manifestations for BS based on the presence of recurrent oral aphthous ulcers, genital ulcers, dermatological findings, and/or uveitis and evidence for myocardial infarction based on ECG findings, elevated troponin levels, and/or angiogram findings were selected for analysis. Data was extracted using predefined criteria.

Main Points

- Acute coronary syndrome in patients with Behcet's syndrome tends to occur in young men.
- These patients often lack traditional coronary artery disease risk factors, although 21% were smokers.
- Chest pain and ST-segment elevation myocardial infarction were the most common findings on presentation.
- Stent restenosis was a common complication in the patients who had percutaneous coronary intervention and stent placement.
- Immunotherapy may be helpful to prevent acute coronary syndrome in these patients.

Results

We identified a total of 62 case reports (16-73). The earliest case report was published in the year 1982. The most common presenting complaint was chest pain, reported in 85% of cases. In addition, the patients with BS presented with dyspnea, epigastric pain, fatigue, arm numbness, presyncope, syncope, nausea, vomiting and leg swelling, palpitation, melena, headache, shoulder pain, and ventricular arrhythmia (Table 1).

In the 47 patients with a diagnosis of BS, 70% developed ACS within 10 years of the BS diagnosis. In fact, BS was diagnosed at the time of presentation in only 26%. The mean duration between diagnosis of BS and presentation of ACS was 7.6±7.9 years. Therefore, ACS may occur before or soon after diagnosis of BS. Pathogenesis of ACS in these patients is probably inflammation and vasculitis rather than accelerated atherosclerosis from the disease or corticosteroids used in treatment.

Table 1. Presenting complaint reported in 62 cases of Vasculo-Behcet's syndrome.

Chief complaint	Number (percentage)
Chest pain	53 (85%)
Dyspnea	6 (9.7%)
Epigastric pain	5 (8.1%)
Fatigue	3 (4.8%)
Arm numbness	3 (4.8%)
Presyncope	1 (1.6%)
Syncope	1 (1.6%)
Nausea/vomiting	1 (1.6%)
Palpitation	1 (1.6%)
Leg swelling	1 (1.6%)
Melena	1 (1.6%)
Headache	1 (1.6%)
Shoulder pain	1 (1.6%)
Ventricular arrhythmia	1 (1.6%)

Multiple analyses have been looked into to define the mean age of ACS in the general population. Mehta et al. (16) in 2016 reported the mean age of ACS as 71.8 and 65 in women and men, respectively, in the United states with the age being lower in the developing countries of the world (women 58.6±11.6 and men 53.0±11.2 years) (74).

ACS occurred mainly in men with BS but at a younger age than expected. Men accounted for 81% of the cases with 84% of the patients being younger than 50 years of age at presentation. The mean age at presentation was 37±12 years.

The most commonly reported manifestations of Behcet's syndrome were oral lesions, urogenital lesions, cutaneous lesions, ocular lesions, pathergy, arthritis, pulmonary involvement, intra-cardiac thrombus, abdominal aortic aneurysm, thoracic aortic aneurysm, and renal involvement. Deep vein thrombosis was reported in 9.7%, pulmonary embolism in 1.6%, and the total incidence of thromboembolism in the group was 11.3%.

Twenty-one percent of the patients had a history of smoking, 6.5% were hypertensive, 4.8% had hyperlipidemia, and none were diabetic. Heart rate and blood pressure values were reported in 21 patients. Mean systolic blood pressure was 114±18 mm Hg. Mean diastolic blood pressure was 68±10 mm Hg. Two of the 62 cases had a family history of ACS. Overall,

Table 2. Type of coronary lesion reported by coronary angiography reported in 50 cases of Vasculo-Behcet's syndrome.

Finding	Number (percentage)
Stenosis	32 (64%)
Aneurysm	26 (52%)
Thrombosis	4 (8%)
Arteritis	3 (6%)
Pseudoaneurysm	3 (6%)
Ectasia	2 (4%)
Fistula	2 (4%)

the prevalence of traditional risk factors for coronary artery disease was low.

Electrocardiography (ECG) findings were reported in 44 patients. ST-segment elevation was reported in 48%, Q waves in 20%, ST-segment depression in 16%, non-specific ST-T changes in 9.1%, T-wave inversion in 6.8%, and acute MI in precordial leads in 4.6%. Other findings included incomplete right bundle branch block (RBBB), RBBB, "NSTEMI", left anterior hemiblock, and premature ventricular complexes. Ventricular arrhythmia was uncommon with ventricular fibrillation reported in 3.2% and ventricular tachycardia in 1.6%. Transthoracic echocardiogram was described in 41 patients of whom 75.6% had wall motion abnormality, and reduced ejection fraction was noted in 14.6%.

As expected, BS patients with ACS had elevated troponin levels. By definition, all cases of ACS should have a time-dependent elevation in the troponin levels (75). Coronary angiography was performed in 58 patients of whom 62.1% had double-vessel disease, 27.6% had single-vessel disease, and 6.9% had triple-vessel disease. Antero-apical aneurysm and right atrial and ventricular masses were reported in one patient each. Coronary lesions were described in 50 patients who had coronary angiography; coronary stenosis and coronary aneurysm were the most common findings (Table 2). In the management of acute coronary syndrome, anticoagulation was used in 54.6%, beta-blocker in 50%, nitrates in 41%, aspirin in 36%, thrombolytic therapy in 36%, dual antiplatelet therapy in 27%, angiotensin converting enzyme inhibitor (ACEI) in 13.6%, tirofiban 9.1%, calcium channel blockers in 4.6%, "anti-lipid therapy" in 4.6%, and abciximab in 4.6%.

Coronary intervention was performed in 63% of the patients in whom percutaneous coronary intervention (PCI) was performed in 27% and coronary artery bypass surgery (CABG) in 35% of the cases. Restenosis was common in these patients. Of the patients who underwent PCI, stents were placed in 18%, and subsequently all these patients had stent restenosis, hence repeat stent placement at the lesion was performed in 18%, and 5.9% subsequently underwent CABG. Of the patients who underwent CABG, one patient who had CABG underwent a repeat CABG.

Management of Behcet's syndrome with corticosteroids, the most commonly used agent, was described in 50 cases. Monotherapy was reported in 40% of the cases with corticosteroid monotherapy in 26%, colchicine monotherapy in 12%, and chlorambucil in 2%. Corticosteroid therapy was administered in 80% of the cases, colchicine in 40%, azathioprine in 26%, cyclophosphamide in 18%, cyclosporine in 8%, chlorambucil in 4%, methotrexate in 4%, interferon alpha in 2%, hydroxychloroquine in 2%, infliximab in 2%, and mycophenolate in 2%.

Death within 90 days was reported in one case and was secondary to cardiac arrest due to ventricular tachycardia.

Clinical and research consequences

Clinicians should have a higher index of suspicion for ACS in BS patients with chest pain than in patients without BS. The patients reported in this systematic review were younger than other patients with ACS and may have undiagnosed or early BS. They may not have traditional risk factors for atherosclerosis except for smoking. These patients have a high rate of re-thrombosis after PCI and CABG and other vascular complications such as abdominal aortic aneurysm. Future research on management of Vasculo-Behcet's syndrome is needed. Optimal management requires immunosuppression and attention to modifiable risk factors.

Conclusion

In this systematic review, we found that ACS in Vasculo-Behcet's syndrome is mostly reported in adult males younger than 65 years old with a low prevalence of coronary artery disease risk factors, such as hypertension and hyperlipidemia. However, 21% of these patients were smokers. ACS may be the presenting feature of BS. STEMI was a common ECG finding, and double-vessel disease was the most common finding on coronary angiography. Most patients required PCI and/or CABG as an intervention, and incidence of stent re-thrombosis was high in patients with BS. Our study has several limitations. Due to the retrospective systematic review design, we cannot confirm fulfillment of diagnostic criteria for Behcet syndrome in all cases. The cases may also mostly include subjects in academic centers who receive tertiary care. There is no data on follow-up and effect of therapy on patient outcomes. In general, the literature may underestimate the prevalence of cases of ACS in BS due to reporting bias. ACS in BS is an important manifestation of the disease because of high risk for morbidity.

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