The clinical characteristics and outcome of intracardiac thrombus and aortic valvular involvement in Behçet's disease: an analysis of 20 cases

Y.-L. Zhu[1], Q.-J. Wu[2], L.-L. Guo[1], L.-G. Fang[1], X.-W. Yan[1], F.-C. Zhang[2], X. Zhang[2]

[1]Department of Cardiology, [2]Department of Rheumatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences, Beijing, China.

*Yan-Lin Zhu, MD
*Qing-Jun Wu, MD
Li-Lin Guo, MD
Li-Gang Fang, MD
Xiao-Wei Yan, MD
Feng-Chun Zhang, MD
Xuan Zhan, MD

*These authors contributed equally to this work.

Please address correspondence to:
Prof. Xuan Zhang,
Department of Rheumatology,
Peking Union Medical College Hospital,
Peking Union Medical College,
Chinese Academy of Medical Sciences,
Beijing 100730, China.
E-mail: zxpumch2003@yahoo.com.cn

Received on March 9, 2012; accepted in revised form on July 11, 2012.

Clin Exp Rheumatol 2012; 30 (Suppl. 72): S40-S45.

Key words: Behçet's disease, cardiac thrombus, aortic valve

Competing interests: none declared.

ABSTRACT

Objective. *To assess the clinical characteristics and outcome of patients with cardiac Behçet's disease(BD).*

Methods. *Medical charts of 20 cardiac BD patients admitted in Peking Union Medical College Hospital from June 1996 to June 2011 were systematically reviewed, including demographic data, clinical features, laboratory and histopathology findings and outcome.*

Results. *Patients age ranged 19~57 yrs[mean (35±10) yrs], included 17 males and 3 females. Six (30%) of them did not fulfill the ISG criteria at cardiac onset, and fourteen (70%) of them experienced heart failure. Echocardiography findings included intracardiac thrombus (n=7), and aortic valve involvement with left ventricular enlargement and severe aortic regurgitation (n=13). Eight patients underwent surgery before efficient immunosuppressant treatment, and five (62.5%) underwent re-operation due to recurrence of thrombus or valvular dehiscence and severe paravalvular leakage. Histopathology findings revealed predominantly inflammatory cells infiltration, thrombus and fibrous tissue formation. After initiation of prednisone plus immunosuppressant, patients were followed up for 6~42 months (mean 14.8±9.9 months), the intracardiac thrombus disappeared or decreased in size in five cases, remained stable after surgery in the other two cases, and the heart failure disappeared in all patients with aortic involvement.*

Conclusion. *Cardiac BD affects males more than females, and is prone to delayed diagnosis because some patients do not have typical clinical manifestations at cardiac onset; Corticosteroids plus immunosuppressants reduce the thrombus and improve aortic regurgitation and heart failure in cardiac BD, whereas surgery alone does not lead to complete resolution.*

Introduction

Behçet's disease (BD) is a systemic inflammatory vasculitis of unknown etiology, characterised by relapsing episode of oral aphthous ulcers, genital ulcers, cutaneous and ocular lesions as well as other manifestations, such as cardiovascular, neurological and gastrointestinal involvements (1, 2). It has been increasingly recognised that cardiac BD which is relatively rare but leads to poor prognosis, can manifest as valvular, myocardial and coronary lesions, intracardiac mass, pericarditis, as well as conduction system abnormality (1, 3-5). In this study, we analysed the clinical and laboratory manifestations, histopathological finding, as well as treatment and outcome of BD patients with intracardiac thrombus and aortic valve lesions so as to improve our awareness and management of these relatively rare but severe complications of BD.

Patients and methods

Patients and data collection

A total of 405 BD patients (260 male and 145 female) with a mean age of (32±18) years (10~79 years) were admitted in Peking Union Medical College Hospital (PUMCH) from June 1996 to June 2011. Those cases with clinical manifestations suggested of cardiac involvement were assessed with cardiac echocardiography, and 20 of them were identified as having intracardiac thrombus or aortic valvular involvement and were enrolled in this study, including seventeen males and three females, with a mean age of (35±10) years old (19~57 years). Medical charts were systematically reviewed, including demographic data, clinical features, laboratory findings including HLA-B5 and pathergy test. In addition, transthoracic echocardiography was conducted in all patients, and histopathology findings of the resected lesions (n=13) per-

formed on eight patients due to cardiac BD were examined.

Diagnostic criteria

Among the twenty patients with cardiac involvements, fourteen of them fulfilled the International Study Group (ISG) for Behçet's disease criteria that required the presence of oral ulceration in addition to any two of the following manifestations (6): genital ulceration, ocular involvement, positive pathergy test, or skin manifestations (erythema nodosum, papulopustular lesions, acneiform nodules, pseudofolliculitis). In the other six cases, though they did not completely meet the ISG criteria, five presented oral ulceration and skin lesion and one had genital ulceration and skin lesion in addition to cardiac manifestation, and there was no evidence suggested other diseases. They were unanimously diagnosed by three rheumatologists (Q.-J. Wu, F.-C. Zhang, X. Zhang) as having BD and were also included in this cohort of study.

Response criteria

There was no active extracardiac manifestation of BD, the size of thrombus was reduced, and the heart failure improved and the aortic valvular abnormality was stable. Complete remission was defined if thrombus disappeared or there was no recurrence after surgery, no paravalvular leakage after aortic valve replacement or heart failure.

Table I. Extracardiac manifestations of the twenty patients with cardiac BD.

Pt. n.	Sex	Age	BD diagnosis criteria	Delayed diagnosis
1	M	23	Oral ulceration; Genital ulceration; Erythema nodosum; Positive pathergy test; Polyarthritis; Fever	Yes
2	F	21	Oral ulceration; Genital ulceration; Erythema nodosum; Positive pathergy test	No
3	M	35	Oral ulceration; Genital ulceration; Positive pathergy test	No
4	M	19	Oral ulceration; Genital ulceration; Erythema nodosum; Fever	No
5	M	37	Oral ulceration; Genital ulceration; Erythema nodosum; Fever	Yes
6	M	35	Oral ulceration; Uveitis; Acneiform nodules; Positive pathergy test; Fever	Yes
7	M	19	Oral ulceration; Retinal periphlebitis; Papulopustular lesions; Fever	No
8	M	43	Oral ulceration; Genital ulceration; Erythema nodosum	Yes
9	M	37	Oral ulceration; Papulopustular lesions; Fever	Yes
10	M	33	Oral ulceration; Papulopustular lesions; Positive pathergy test; Cerebral infarction	No
11	M	38	Oral ulceration; Genital ulceration; Pseudofolliculitis; Positive pathergy test	No
12	M	35	Genital ulceration; Pseudofolliculitis; Fever	Yes
13	M	26	Oral ulceration; Genital ulceration; Acneiform nodules	Yes
14	F	37	Oral ulceration; Genital ulceration; Uveitis; Erythema nodosum	No
15	M	47	Oral ulceration; Acneifor nodules; Fever	No
16	M	47	Oral ulceration; Genital ulceration; Pseudofolliculitis	No
17	M	44	Oral ulceration; Genital ulceration; Erythema nodosum; Arthritis; Cerebral infarction	No
18	M	57	Oral ulceration; Papulopustular lesions	Yes
19	M	34	Oral ulceration; Pseudofolliculitis; Fever	Yes
20	F	39	Oral ulceration; Erythema nodosum	No

Results

Clinical manifestations and diagnosis

Classical manifestations of these twenty cardiac BD patients included oral ulceration (n=19), genital ulceration (n=12), ocular involvement (n=3), skin lesions (n=19), and positive pathergy test (n=6), as listed in Table I. Other extracardiac involvements included fever (n=9), other vascular lesions (n=6), arthritis (n=2), cerebral infarction (n=2). No patient had gastrointestinal involvement or familial history of BD. Positive HLA-B5 was noted only in one of the twelve patients tested. The levels of erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were significantly elevated in eleven and twelve patients, respectively.

Intracardiac thrombus was found in seven patients. In three of them, thrombus occurred as presenting manifestation 6 to 12 months prior to other symptoms, and in the other four patients, it was found 18 to 26 months after the onset of BD. The main symptoms in these seven patients were chest pain, hemoptysis, cough and dyspnea, which was associated with pulmonary embolism or pulmonary occlusion. Five patients had fever and large artery involvements. Four patients had deep venous thrombosis (Table II). Laboratory tests for thrombophilia, including antiphospholipid antibodies (anti-cardiolipin antibody, anti-β2 glycosidoprotein 1 antibody, and lupus anticoagulant), genetic procoagulant factors (protein S, protein C, antithrombin III, activated protein C resistance, factor V Leiden mutation) were performed in seven and five cases with intracardiac thrombus, respectively, and most of these tests were negative except that lupus anticoagulant was positive in two patients.

Aortic valve lesion was the main cardiac manifestation in the other thirteen patients, and twelve of them experienced left heart failure manifested as dyspnea and cough, and diagnosis of BD was delayed 1 to 24 months in eleven (85%) patients because patients did not fulfill the ISG criteria for BD at the onset of aortic valve regurgitation. Only one patient had aortic and subclavian artery aneurysm (Table III).

Echocardiography

Transthoracic echocardiography was conducted in all patients. Intracardiac thrombus were found only in the right cavity in four patients (Fig. 1A and Fig. 1B), only in the left cavity in one patient (Fig. 1C), and in both left and right cavities of the heart in two patients, as listed in Table II. The thrombus masses were attached to the free

Table II. Clinical and echocardiographic manifestations, treatment and outcome of the seven BD patients with intracardiac thrombus.

	Clinical manifestation	Location of intracardiac thrombus	Other vascular involvement	Treatment	Follow-up
1	Chest pain; Haemoptysis	RV	Anterior and posterior tibial pseudoaneurysm; Iliac and popliteal venous thrombus; PE	Cardiac surgery; P 60mg/d; CYP 1g/4w iv; Warfarin	8 months; complete remission
2	Chest pain	LV	Abdominal aortic pseudoaneurysm; PE	P 60mg/d; CYP 0.4g/w iv; Warfarin	6 months; improvement
3	Abdominal pain; Distension; Back pain	RA	Abdominal aortic pseudo-aneurysm; Inferior vena cava, bilateral iliac and femoral vein, portal venous thrombus; PE	P 60mg/d; Cys 200mg/d; Warfarin	42 months; complete remission
4	Cough; Dyspnea; Haemoptysis	RA, RV	Superior and inferior vena cava thrombus; PE	P 50mg/d; CYP 0.4g/m iv; Warfarin	10 months; improvement
5	Cough	RV	No	Cardiaic surgery; P 60mg/d; CYP 0.4g/w iv; Warfarin	8 months; complete remission
6	Chest pain; Dyspnea	RA, LV	No	Cardiac surgery; P 60mg/d; CYP 0.6g/w iv; Warfarin	9 months; improvement
7	Cough; Chest pain; Haemoptysis	RV, LV	Inferior vena cava, left iliac vein and bilateral renal venous thrombus; PE	P 30mg/d; CYP 50mg/d; Warfarin	12 months; complete remission

RV: right ventricle; LV: left ventricle; RA: right atrium; PE: pulmonary embolism; P: prednisone/predinisolone; CYP: cyclophosphamide; Cys: cyclosporine A.

Table III. Clinical and echocardiographic manifestations, treatments and outcomes of the thirteen patients with cardiac valve involvements

	Heart failure	Echo findings	Medicine treatment	Surgery	Follow-up
1	Yes	Ascending aortic dilation; Redundant coronary cusps motion; Vegetation-like lesions; Echo-free spaces; Paravalvular leakage after 1st AVR	P 50mg/d; CYP 1g/4w iv	AVR 2 times (1st complicated paravalvular leakage without immunosupressant)	23 months; improvement
2	Yes	Aortic aneurismal dilatation; Vegetation-like lesions; Echo-free spaces; Paravalvular leakage after AVR (two times)	P 10mg/d (1st), 30mg (2nd); CYP 50mg/d	AVR 2 times (both complicated paravalvular leakage without immunosupressant)	Lost to follow-up
3	No	Aortic aneurismal dilatation; Redundant coronary cusps motion	P 60mg/d; Cys 300mg/d; CYP 100mg/d	No	6 months; improvement
4	Yes	Ascending aortic dilation	P 40mg/d; CYP 100mg/d	No	14 months; improvement
5	Yes	Vegetation-like lesions	P 60mg/d; CYP 0.4g/w iv	AVR complicated vegetation and paravalvular leakage without immunosupressant	12 months; clinically stable
6	No	Ascending aortic dilation	P 50mg/d; CYP 0.6g/w iv	No	9 months; improvement
7	Yes	Redundant coronary cusps motion	P 45mg/d; CYP 0.6g/w iv	No	23 months; clinically stable
8	Yes	Redundant coronary cusps motion	P 50mg/d; CYP 100mg/d	No	17 months; improvement
9	Yes	Redundant coronary cusps motion	P 55mg/d; CYP 100mg/d	No	31 months; improvement
10	Yes	Severe aortic regurgitation	P 70mg/d; CYP 100mg/d	No	7 months; improvement
11	Yes	Redundant coronary cusps motion; Echo-free spaces; Paravalvular leakage after AVR	P 50mg/d; CYP 0.4g/w iv	AVR complicated paravalular leakage without immunosuppressant	Lost to follow-up
12	Yes	Aortic aneurismal dilatation; Echo-free spaces; Paravalvular leakage after AVR(two times)	P 60mg/d; MTX 15mg/w; CYP 0.8g/2w	AVR 2 times , both with paravalvular leakage before BD diagnosis	Lost to follow-up
13	Yes	Vegetation-like lesions	P 45mg/d; Cys 200mg/d	No	15 months; improvement

P: prednisone/predinisolone; CYP: cyclophosphamide; Cys: cyclosporine; MTX: methotrexate; AVR: aortic valve replacement.

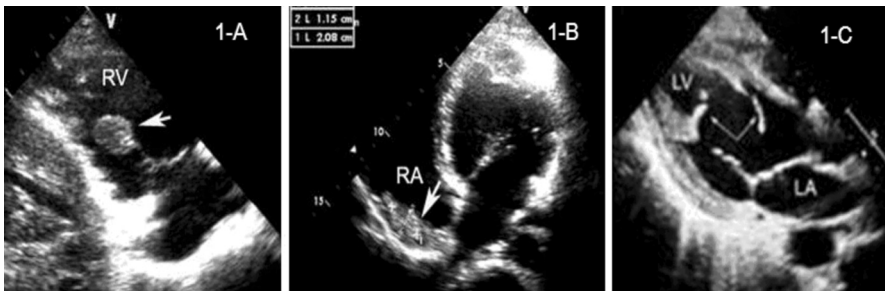

Fig. 1. A: mass in right ventricle; B: mass in right atrium; C: mass in left ventricle.

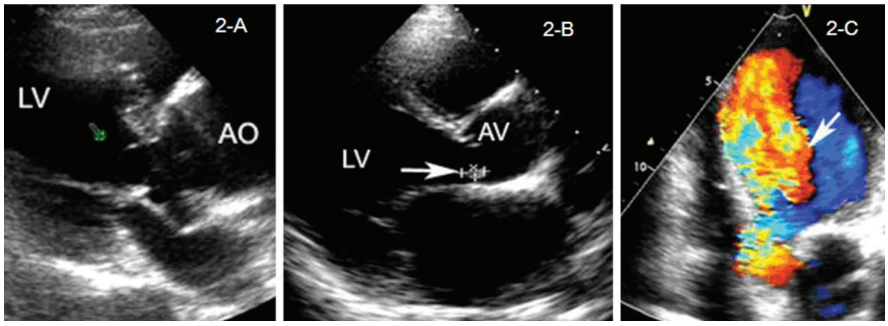

Fig. 2. A: redundant coronary cusp motion; B: vegetation-like lesions; C: severe aortic regurgitation.

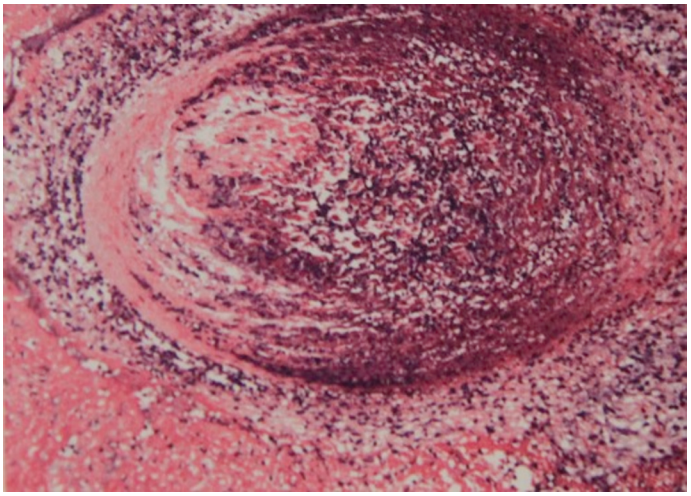

Fig. 3. The myocardium underlying the attachment of the intracardiac mass was infiltrated by inflammatory cells.

wall or the septum, extended into the superior or inferior vena cava, and their size varied from 6 to 49 mm, with an average of 23 mm. They presented as multiple masses within one chamber or occurred in more than one chamber in three patients. The thrombus mass was associated with tricuspid valve involvement in one patient, in another patient interfered with the functional integrity of the mitral valve, and led to heart failure in two patients.

Transthoracic echocardiography in the other thirteen BD patients with aortic valve involvement also revealed that three (23%) had aortic aneurismal dilatation with enlarged annulus of the aortic valve, and six patients (46%) had redundant coronary cusp motion (Fig. 2A). In eight patients (62%), echocardiography findings mimicked that of infectious endocarditis, manifested as vegetation-like lesions or echo-free spaces similar to abscess pockets in four patients each (Fig. 2B) albeit with negative finding on blood culture. Left ventricular enlargement and severe aortic regurgitation (Fig. 2C) were observed in all these thirteen patients, as listed in Table III.

Histopathology

A total of 13 operations were performed on 8 patients due to cardiac BD. Histopathology findings of the resected mass (n=3) or aortic valve (n=5) revealed predominantly lymphocytes infiltration and thrombus or mainly fibrous tissue with inflammatory cells infiltration that contained a mixture of granulocytes, mononuclear inflammatory cells. The myocardium underlying the attachment of the intracardiac thrombus was either normal or infiltrated by inflammatory cells extending from the overlying thrombus (Fig. 3). Examination of the resected aortic valves revealed that the inflammation caused tissue fragility and completely destroyed the original aortic valves.

Treatment, clinical course and outcomes

Eight patients underwent surgery because of severe intracardiac thrombus or aortic valve regurgitation, that occurred before definite or probable BD diagnosis was established (n=6) or because the patients were incompliance to moderate dosage of corticosteroid uncombined with immunosuppressive reagents (n=2), and five (62.5%) of them underwent re-operation due to recurrence of intracardiac thrombus (n=1) or valvular dehiscence and severe paravalvular leakage (n=4) developed after the first surgery, and two with paravalvular leakage for two times after surgery, as listed in Table II and III.

Once the cardiac lesion was diagnosed as part of BD, prednisone (1mg/kg/d) plus cyclophosphamide (n=18), and/or cyclosporine A (n=3) and methotrexate (n=1) were initiated, and warfarin for anticoagulation was used for patients with intracardiac thrombus during follow-up, diuretics added to patients with heart failure caused by aortic valve regurgitation. Prednisone was gradually tapered and immunosupressants were used during follow-up. Seventeen patients were followed up for 14.8±9.9 months (6~42 months), three were lost. The intracardiac thrombus disappeared in two cases, remained stable after surgery without recurrence in two cases, and decreased in size in the other three patients. The condition improved in all patients with aortic involvement after treatment with prednisone plus immu-

nosuppressant, and heart failure disappeared in all cases followed up, as listed in Table II and III. No patient died during follow-up.

Discussion

Cardiac involvement is usually encountered in 1%-7% of patients with BD (1, 4, 7-9). Complication of intracardiac thrombus seems to occur predominantly in patients from the Mediterranean basin and the Middle East (3), suggesting a role of genetic predisposition in specific organ involvement (7). Epidemiological surveys indicate that male and female are equally affected by BD, whereas in severe disease female is far outnumbered by male (1), which was also demonstrated in our case series of cardiac BD that predominantly affected male patients.

Inflammatory destruction and vasculitis are the basis of cardiac BD that lead to aortic aneurismal dilatation, characteristic redundant coronary cusps motion, vegetation-like lesions and paravalvular abscess pockets (4, 10-12). The major histopathological findings in our series were also inflammatory cells infiltration, thrombus and fibrous tissue formation. The underlying mechanism of intracardiac mass formation in BD has not been fully clarified. It may be due to endothelial dysfunction, endocardial fibrosis, platelet activation, enhanced thrombin and fibrin generation, imbalance of coagulation and fibrinolytic system (3-5, 13, 14). Antiphospholipid antibodies has a causative role in the intracardiac thrombi formation (3). Lupus anticoagulant was detected in two of the seven patients. Most mass lesion especially thrombus in BD occur in the right cavity (4, 13-15), as also found in our series. As one of the factors in the development of intracardiac thrombus, endomyocardial fibrosis usually affected the right heart (9). Other possible explanation may be due to extension of vena cava thrombosis or akinetic state of right-side cavity. However, three of the seven patients (43%) had thrombus in the left-side chamber. According to the histopathological findings after surgery, inflammation was the basis of thrombus, as demonstrated by series of studies (3-5, 14).

In the current survey, 86% (6/7) BD patients with intracardiac thrombus also had pulmonary artery involvement, including pulmonary embolism or multiple pulmonary occlusion. The main type of pulmonary artery involvements in patients with BD was pulmonary embolism which was strongly associated with deep venous thrombosis and indicated good response to anticoagulation (3, 16). Pulmonary embolism was confirmed by computerised tomography of pulmonary artery (CTPA) or V/Q in five patients, five with right chamber thrombus, four with deep venous thrombus. One patient had pulmonary occlusion, with left ventricular thrombus and without deep venous thrombosis. Pulmonary artery aneurysm or stenosis/occlusion caused by vasculitis usually resolved after immunosuppressive treatment rather than anticoagulation (3, 16).

Cardiac involvement is an uncommon complication of BD, and our study revealed that less one third of the patients did not have typical clinical manifestations that fulfilled the ISG criteria at the onset of cardiac symptoms, thereby led to delayed diagnosis of cardiac BD, suggesting the most commonly adopted ISG diagnostic criteria is not suitable for prompt diagnosis of cardiac BD. Our study showed that the delayed diagnosis and immunosuppressant administration led to destruction of elastic structures of aorta resulting in formation of aneurysms and pseudoaneurysms prone to rupture. Also recurrent thrombus or valvular dehiscence and severe paravalvular leakage could develop in short time after surgery, which worsened cardiac function (10, 17). Echocardiography is helpful in identifying early lesions and examining the severity and extent of cardiac BD in suspected patients (3, 4, 8, 10, 12, 18). In our study, the intracardiac thrombus was either attached to the free wall or the septum, varied in size, sometimes multiplied in one chamber or affected multiple chambers, and could interfered with the functional integrity of the mitral valve or tricuspid valve. Our study also found that under echocardiography examination, nearly 50% patients with aortic valve regurgitation had aneurismal formations with redundant coronary cusps motion that was pathognomonic for BD, which had not been previously reported in other diseases and might have been due to the inflammatory destruction of cusps (10-12). Some echocardiography findings, such as vegetation-like lesions and echo-free spaces indistinctable from infectious endocarditis, were also observed in our study. As immunosuppressive therapy required for BD conflicts with treatment strategy for infectious endocarditis, differential diagnosis is indispensable. Futility of blood and/or tissue culture together with an underlying valvular pathology of aortic regurgitation, plus inefficacy with antibiotics treatment, will help us to exclude the diagnosis of infectious endocarditis.

In the current study, eight patients underwent surgery for thirteen times. They did not receive efficient immunosuppressive treatment before the operation. We found that corticosteroids plus immunosuppressive reagents were pivotal in the treatment of cardiac BD (4, 10, 14, 15, 18-21), whereas surgery alone did not lead to complete resolution, and recurrence was common (62.5%) (14, 15, 19, 20), and we suggest effective control of the underlying vasculitis with immunosuppressant before cardiac surgery to prevent unwanted complications. Regarding intracardiac thrombus and/or deep venous thrombus, the benefit of anticoagulation is controversial. Anticoagulation, accompanied with immunosuppressant treatment, may be indicated for patient without bleeding tendency (22).

In conclusion, cardiac BD including intracardiac thrombus and aortic valvular involvement affects males more than females, and is prone to delayed diagnosis because about one third of patients do not have typical clinical manifestations that fulfill the ISG criteria at cardiac onset. Echocardiography is helpful in identification of cardiac BD. Corticosteroids plus immunosuppressant reduce the thrombus and improve aortic regurgitation and heart failure in cardiac BD, whereas surgery alone does not lead to complete resolution.

References

1. AZIZLERLI G, KOSE AA, SARICA R *et al*.: Prevalence of Behçet's disease in Istanbul, Turkey. *Int J Dermatolo* 2003; 42: 803-6.
2. SAKANE T, TAKENO M, SUZUKI N *et al*.: Behçet's disease. *N Engl J Med* 1999; 341: 1284-91.
3. MOGULKOE N, BURGESS MI, BISHOP PW: Intracardiac thrombus in Behçet's disease: a systematic review. *Chest* 2000; 118: 479-87.
4. LEE I, PARK S, HWANG I *et al*.: Cardiac Behçet disease presenting as aortic valvulitis/aortitis or right heart inflammatory mass: a clinicopathologic study of 12 cases. *Am J Surg Pathol* 2008; 32: 390-8.
5. LEIBA M, SIDI Y, GUR H *et al*.: Behçet's disease and thrombophilia. *Ann Rheum Dis* 2001; 60: 1081-5.
6. INTERNATIONAL STUDY GROUP FOR BEHÇET'S DISEASE: Criteria for diagnosis of Behçet's disease. *Lancet* 1990; 335: 1078-80.
7. EHRLICH GE: Vasculitis in Behçet's disease. *Int Rev Immunol* 1997; 14: 81-8.
8. LIE JT: Cardiac and pulmonary manifestations of Behçet syndrome. *Pathol Res Pract* 1988; 183: 347-55.
9. HUONG DL, WECHSLER B, PAPO T *et al*.: Endomyocardial fibrosis in Behçet's disease. *Ann Rheum Dis* 1997; 56: 205-8.
10. AHN JK, KIM H, LEE J *et al*.: Treatment outcomes in patients with non-infectious aortic valvulitis undergoing aortic valve replacement: implication for the treatment of aortic valve involvement in Behçet's disease. *Rheumatol Int* 2009; 29: 1391-3.
11. HAN JK, KIM HK, KIM YJ *et al*.: Behçet's disease as a frequently unrecognized cause of aortic regurgitation: suggestive and misleading echocardiography findings. *J Am Soc Echocardiogr* 2009; 22: 1269-74.
12. LEE CW, LEE J, LEE WK *et al*.: Aortic valve involvement in Behçet's disease. A clinical study of 9 patients. *Korean J Intern Med* 2002; 17: 51-6.
13. KAJIYA T, ANAN R, KAMEKO M *et al*.: Intracardiac thrombus, superior vena csva syndrome, and pulmonary embolism in a patient with Behçet's disease: a case report and literature review. *Heart Vessels* 2007; 22: 278-83.
14. KANEKO Y, TANAKA K, YOSHIZAWA A *et al*.: Successful treatment of recurrent intracardiac thrombus in Behçet's disease with immunosuppressive therapy. *Clin Exp Rheumatol* 2005; 23: 885-7.
15. HAZNEDAROGLU IC, OZCEBE O, CELIK I *et al*.: Haemostatic marker of procoagulant imbalance in Behçet's disease. *Eur J Haematol* 1996; 57: 107-8.
16. SEYAHI E, MELIKOGLU M, AKMAN C *et al*.: Pulmonary artery involvement and associated lung disease in Behçet disease: a series of 47 patients. *Medicine* 2012; 91: 35-48.
17. AZUMA T, YAMAZAKI K, SAITO S *et al*.: Aortic valve replacement in Behçet's disease: surgical modification to prevent valve detachment. *Eur J Cardiothorac Surg* 2009; 36: 771-2.
18. HUANG XM, HUANG CJ, SHA Y *et al*.: Cardiac valve involvement in Behçet's disease: a clinical study of 10 patients. *Zhonghua Yi Xue Za Zhi* 2010; 90: 2357-9.
19. DINCER I, DANDACHI R, ATMACA Y *et al*.: A recurrent right heart thrombus in a patient with Behçet's disease. *Echocardiography* 2001; 18: 15-8.
20. SVENNEVIG JL, ABDELNOOR M, NITTER-HAUGE: Twenty-five year experience with the Medtronic-Hall valve prosthesis in the aortic position: a follow-up cohort study of 816 consecutive patients. *Circulation* 2007; 116: 1795-800.
21. SACRE K, DUCROCQ G, HERNIGOU A *et al*.: Unusual cardiovascular events in Behçet's disease. *Clin Exp Rheumatol* 2010; 28: S82-5.
22. HATEMI G, SIMAN A, BANG D *et al*.: EULAR recommendations for the management of Behçet disease. *Ann Rheum Dis* 2008; 67: 1656-62.