Echocardiographic findings of cardiovascular involvement in Behçet's disease and post-operative complications after cardiac surgery

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ABSTRACT

Objective. *The aim of this study was to analyse the spectrum of echocardiographic findings in patients with cardiovascular involvement in Behçet's disease (BD) and followed up the post-operative complications.*

Methods. *We enrolled 26 BD patients who underwent first cardiac surgery in Anzhen Hospital, Beijing, China. Medical records and echocardiographic findings were retrospectively analysed.*

Results. *The 26 patients consisted of 4 women and 22 men. 22 (84.6%) of the patients were diagnosed with moderate/severe aortic regurgitation (AR). Some distinctive echocardiographic features with AR were observed, including prolapse of aortic cusps, vegetation-like mobile lesions, an echo-free space mimicking aortic root abscess and aortic aneurysm formation. 3 (11.5%) of the patients was diagnosed with isolated descending aortic aneurysm.1(3.8%) of the patients was diagnosed with pulmonary artery aneurysm. BD was preoperatively diagnosed by clinicians in 20 patients. And 6 patients were diagnosed postoperatively by clinicians. In a total of 26 patients, postoperative complications occurred in 8 (30.7%) patients. The complications occurred in the 6 patients diagnosed postoperatively and 2 patients diagnosed preoperatively. The postoperative complications of these patients included aortic paravalvular leakage, coronary-graft anastmotic leakage and mitral paravalvular leakage.*

Conclusion. *The most common echocardiographic feature of cardiovascular involvement in BD is severe aortic regurgitation with prolapse of aortic cusps, vegetation-like mobile lesions, an echo-free space mimicking aortic root abscess or aortic aneurysm formation. Accurate preoperative diagnosis of BD is beneficial to the choice of immunosuppressive therapy before and after surgery, which is likely to reduce postoperative complications especially for patients with severe lesions.*

Introduction

Behçet's disease (BD) is a chronic, relapsing autoimmune disorder characterised by recurrent oral and genital ulcers and variable multiple-organ involvement. It is found worldwide, but has been reported to be most common in the countries of Middle East and Asia (1). The pathophysiology involves active inflammation of large and small arteries. It is believed cardiac involvement is one of the most severe complications in patients with BD (2, 3). The incidence and natural history of cardiac involvement in this disorder are not yet clearly documented. Estimates of cardiovascular involvement in BD have been reported between 7% and 46%, with lethal outcomes in about 20% of severe cases (4). Our previous studies revealed that the most common cardiac lesion were aortic regurgitation, aortic lesions such as aortic dilatation, aortic pseudoaneurysm and sporadic cases of intracardiac thrombosis and coronary pseudoaneurysm (5). The possible diagnosis of BD should be considered when evaluating patients with these echocardiographic manifestations. Surgical treatment of BD with associated severe aortic regurgitation (AR) is very often difficult because the aortic tissue involved is routinely inflamed and extraordinarily fragile. For this reason, post-operative complications including haemorrhage, pseudoaneurysm formation, valve detachment, and paravalvular leakage are frequent and life threatening, requiring redo operations in many patients (6, 7). At present some research indicated that aortic root

Table I. Clinical characteristics and fulfillment of the diagnostic criteria (ICBD) for BD.

Patient	Age/sex	Preoperative diagnosis	Oral aphthosis	Genital aphthosis	Ocular lesions	Skin lesion	Vascular manifestations	Central nervous system involvement	Pathergy test	Point
1	25/M	No	+		+					4
2	40/M	Yes	+			+	+			4
3	46/M	Yes		+	+	+				5
4	44/F	Yes	+		+		+			5
5	31/M	No	+			+	+			4
6	42/M	No	+			+	+			4
7	37/M	Yes	+	+					+	5
8	38/M	Yes	+			+			+	4
9	34/M	Yes	+	+	+		+			7
10	52/F	Yes	+			+	+		+	5
11	30/M	Yes	+	+		+				5
12	32/M	Yes	+			+	+			4
13	36/M	Yes	+			+	+			4
14	38/M	Yes	+			+	+			4
15	42/F	Yes	+	+	+	+				7
16	38/M	Yes	+			+			+	4
17	42/M	Yes	+			+	+			4
18	51/M	Yes	+			+	+			4
19	35/M	No	+	+		+				5
20	25/M	No	+			+	+			4
21	28/M	Yes	+	+		+	+			6
22	45/F	Yes	+	+		+	+			6
23	26/M	Yes	+			+	+			4
24	21/M	No	+	+						4
25	52/M	Yes	+	+						4
26	52/M	Yes	+			+			+	4

Table II. Baseline characteristics of Behçet's disease patients with cardiac involvement.

Features	(n=26)
Epidemiological features	
Age (years)	37 ± 8
Male, no. (%)	22 (84.6%)
Female, no. (%)	4 (15.4%)
Clinical features	
Oral ulceration	25 (96.2%)
Genital ulceration	10 (38.5%)
Ocular involvement	5 (19.2%)
Skin lesions	20 (76.9%)
Vascular lesions	15 (57.7%)
Positive pathergy	5 (19.2%)
Cardiac symptoms	
Chest distress, no. (%)	16 (61.5%)
Chest pain, no. (%)	2 (7.6%)
Dyspnea, no. (%)	2 (7.6%)
Fever, no. (%)	2 (7.6%)
Fatigue, no. (%)	3 (11.5)
Haemoptysis, no. (%)	1 (3.8%)
Laboratory features	
ESR (mm/1st hour)	24.75 ± 17.97
hsCRP (mg/L)	16.80 ± 13.57

replacement (ARR) should be the procedure of choice for surgical treatment of AR, instead of simple aortic valve replacement in BD. Moreover, pre-operative and/or post-operative steroids and immunosuppressive therapy have been proven to be beneficial to control inflammation and prevent post-operative complications of BD (6, 8). Therefore, the pre-operative recognition of cardiac involvement in BD is paramount. Many sporadic case reports have described the cardiac involvement in BD in the literature, but few have specifically reported the echocardiographic manifestation for the pre-operative cardiovascular damage and post-operative complications after cardiac surgery (9, 10). Outcomes may be improved by early diagnosis on the basis of characteristic echocardiographic features and/or pathologic findings. In this article we analysed the spectrum of echocardiographic findings in 26 patients with cardiovascular involvement in BD and followed up the post-operative complications.

Materials and methods

Study participants

A retrospective review of clinical database in Beijing Anzhen Hospital from January 2003 to December 2016 was performed and 98 BD patients were identified. Among these BD patients, 43 underwent cardiac surgical treatment in our Hospital; we had excluded 14 patients who underwent the first cardiac operations in other hospitals and 3 patients who had no complete pre-operative and post-operative echocardiographic data. Finally, we enrolled 26 patients who underwent first cardiac surgery in our hospital and had complete pre-operative and post-operative clinical and echocardiographic data. The 26 patients with cardiac involvement in BD were identified on the basis of their clinical symptoms, laboratory tests, intra-operative findings and pathologic examinations. The Ethics Committee of Beijing Anzhen Hospital and Cardiovascular Institute approved this retrospective study and waived the need for individual patient consent for this study. For each patient clinical records, including the clinical symptoms, inflammation markers and echocardiographic studies, were retrospectively analysed. The clinical data included age, sex, and cutaneous ulcers (genital and oral), eye, central nervous system, vascular involvement. Inflammation

markers included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP).

Imaging protocols of transthoracic echocardiography (TTE)

All patients underwent a complete transthoracic two-dimensional and Doppler echocardiography using a 2.0 to 5.0MHz transducer with GE Vivid7 and Philips IE33 ultrasound systems. The echocardiographic images included the parasternal left ventricular long axis view, large artery short axis view, apical four-chamber view, suprasternal view, subcostal view and some modified, non-standard views. The anatomical structure of the heart was probed carefully in these views so as to confirm whether there were cardiovascular anomalies.

Follow-up data

All patients underwent surgical intervention. The timing of surgery and the perioperative administration of anti-inflammatory drugs were determined by the attending physician after consultation with cardiac surgeons and rheumatologists. The type of surgery was also determined by a cardiac surgeon. Pathologic examination of the surgical specimens showed aortic valvulitis with fibrinous deposits, microabscesses, and extensive endothelial loss, with no evidence of microorganism or infective endocarditis, characteristics compatible with the involvement of BD.

Results

Patient characteristics and cardiac findings

Our study cohort consisted of 26 patients (4 women and 22 men, mean age: 37±8 years). BD had been preoperatively diagnosed in 20 patients, while 6 patients were diagnosed postoperatively.

The demographic variables and BD criteria are shown in Table I. The patients were re-scored according to the International Criteria for Behçet's Disease (ICBD) (11). Ocular lesions, oral aphthosis and genital aphthosis were assigned 2 points each, while skin lesions, central nervous system involvement and vascular manifestations 1 point each. The pathergy test, when used, was assigned 1 point. A patient scoring ≥4 points was classified as having BD. The 26 patients all fulfilled the current ICBD criteria for BD. Classical manifestations of these twenty six cardiac BD patients included oral ulceration (n=25), genital ulceration (n=10), ocular involvement (n=5), skin lesions (n=20), positive pathergy (n=5) and vascular lesions (n=15). Vascular lesions included aortic dilatation/aneurysm, echo-free space mimicking aortic root abscess and pulmonary artery aneurysm, etc. The main symptoms of the patients were chest distress, chest pain, fatigue, dyspnea, fever and haemoptysis. The levels of ESR and CRP were significantly elevated in fifteen and nineteen patients, respectively (Table II).

Table III. Important echocardiographic findings in patients with cardiac involvement in BD.

Important echocardiographic findings	n
Aortic regurgitation	22 (84.6%)
Prolapse of aortic cusps	16
Vegetation-like mobile lesions	4
An echo-free space mimicking aortic root abscess	6
Aortic aneurysm formation	2
Isolated aortic aneurysm	3 (11.5%)
Pulmonary artery aneurysms	1 (3.8%)

Preoperative echocardiographic findings

The characteristic pre-operative echocardiographic manifestations are summarised in Table III, including aortic regurgitation, isolated aortic aneurysm and pulmonary artery aneurysm.

– Aortic regurgitation (AR)

In our study, 22 (84.6%) of the patients were diagnosed with moderate to severe AR. Some distinctive echocardiographic features of AR were observed, including prolapse of aortic cusps, vegetation-like mobile lesions, an echo-free space mimicking aortic root abscess and aortic aneurysm formation.

– Prolapse of aortic cusps

In 22 patients with AR, echocardiography revealed prolapse of aortic cusps in 16 patients (61.5%). Echocardiography showed that the free edge of one or more aortic cusps overrided the plane of the aortic annulus into the left ventricular outflow tract of the distal part of a cusp. The unusual aortic cusps thinning and redundancy were the typical features of the prolapse of aortic cusps (Fig. 1).

– Vegetation-like mobile lesions

In 22 patients with AR, vegetation-mimicking mobile lesions from the aortic valve were observed in 4 patients with severe AR. 3 of them were complicated with prolapse of aortic cusps. These vegetation-mimicking mobile lesions showed oscillating or non-oscillating intracardiac mass on the aortic valve (Fig. 2). In these 4 patients, infective endocarditis were suspected by echocardiography.

– Echo-free space mimicking aortic root abscess

In 22 patients with AR, 6 had annular echo-free spaces within the annulus observed by echocardiography. 3 of them had complications of prolapse of aortic cusps. The annular echo-free spaces showed thickened, non-homogeneous perivalvular area with echoderse or echolucent appearance (Fig. 3). In the 6 patients, infectious endocarditis with aortic root abscess was mimicked by ehocardiography.

– Aortic aneurysm formation

Ascending aortic aneurysm was observed in 2 patients, out of the 22 with AR.

– Isolated aortic aneurysm

3 of the patients (11.5%) were diagnosed with isolated descending aortic aneurysm. Two of them involved descending thoracic aorta, and one of them involved descending thoracic aorta and abdominal aorta.

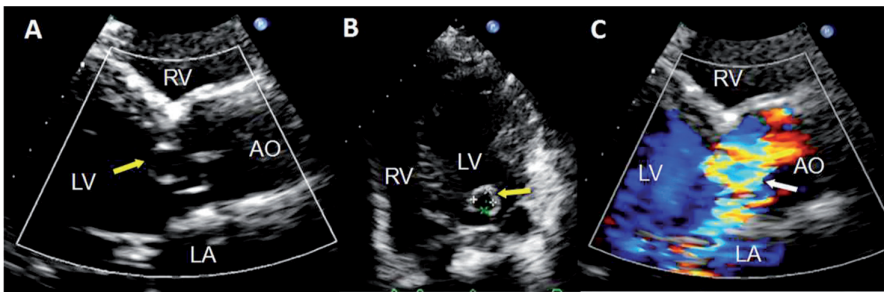

Fig. 1. Transthoracic echocardiography showing severe aortic regurgitation with prolapse of aortic cusps in a BD patient. (**A**) Prolapsed valvular cusps with aneurysmal changes in the aortic valve from parasternal long-axis view (yellow arrow). (**B**) Prolapsed valvular cusps with aneurysmal changes in the aortic valve from apical five chamber view (yellow arrow). (**C**) Eccentric severe aortic regurgitation from parasternal long-axis view (white arrow).
AO: aorta; LA: left atrium; LV: left ventricle; RV: right ventricle.

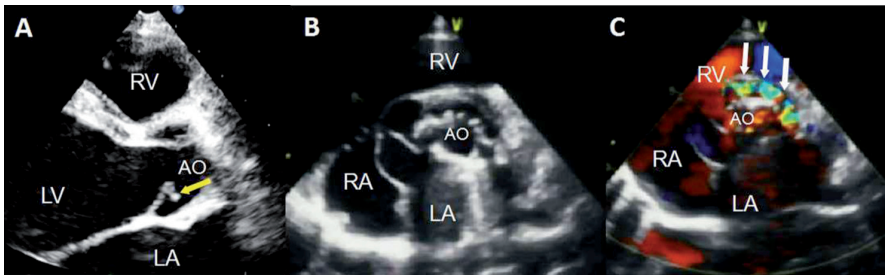

Fig. 2. Transthoracic echocardiography showing severe aortic regurgitation with vegetation-mimicking mobile lesion in a BD patient. (**A**) Vegetation-mimicking mobile lesion in the noncoronary valve from parasternal long-axis view (yellow arrow). (**B**) Mechanical aortic valves in parasternal short-axis view after aortic valve replacement. (**C**) Color Doppler echocardiography showing paravalvular leakage in parasternal short-axis view after aortic valve replacement.
AO: aorta; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle.

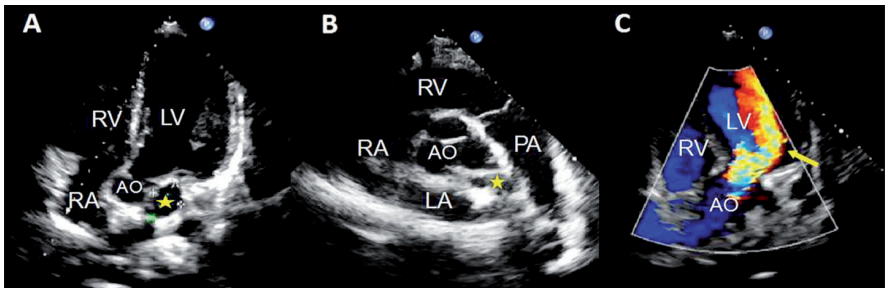

Fig. 3. Transthoracic echocardiography showing severe aortic regurgitation with echo-free space mimicking aortic root abscess in a BD patient. (**A**) The annular echo-free space extending beyond the left coronary sinus from apical five chamber view (yellow star). (**B**) The annular echo-free space extending beyond the left coronary sinus from parasternal short-axis view (yellow star). (**C**) Severe aortic regurgitation from apical five chamber view (yellow arrow).
AO: aorta; LA: left atrium; LV: left ventricle; RA: right atrium; RV: right ventricle; PA: pulmonary artery.

– Pulmonary artery aneurysm
1 patient (3.8%) was diagnosed with pulmonary artery aneurysm.

Treatment and clinical course
26 patients underwent cardiovascular surgery, and BD was pre-operatively diagnosed in 20 of them. They all received pre-operative steroids and/or immunosuppressive therapy to keep the inflammatory makers within the normal range and continued to use the same regimen in the post-operative course. The 6 patients diagnosed post-operatively did not receive steroid and/or immunosuppressive therapy pre-operatively. The initial operations were simple aortic valve replacements (AVR) in 10 cases, Bentall-type operation (composite graft replacement of the aortic valve, aortic root and ascending aorta) in 12 cases, thoracic descending aorta replacement in 2 cases, total thoracic and abdominal aorta replacement in 1 case, transcatheter closure of pulmonary aneurysm in 1 case. Additional operations included mitral valve replacement in 3 cases, mitral valvuloplasty in 5 cases and tricuspid valvuloplasty in 4 cases.

Postoperative complications and echocardiographic findings
In a total of 26 patients, post-operative complications occurred in 8 patients (30.7%) (patients 1, 5, 6, 8, 18, 19, 20 and 24). Complications occurred in 6 patients diagnosed post-operatively (patients 1, 5, 6, 19, 20 and 24) and in 2 patients (8 and 18) diagnosed pre-operatively. The post-operative complications of these patients included aortic mechanical valve dehiscence with severe aortic paravalvular leakage, coronary-graft anastmotic leakage and mitral paravalvular leakage. Table IV shows these post-operative complications and time of complications of these 8 patients. Patients 5, 8, 18 and 19 developed aortic mechanical valve dehiscence with severe aortic paravalvular leakage. Echocardiography showed rocking and dehiscence of the aortic prosthesis and severe paravalvular aortic regurgitation below the valve stent. Patient 8 also developed moderate mitral paravalvular regurgitation and left ventricular-right atrial and right ventricular shunt. Patients 6 and 24 developed severe aortic paravalvular leakage. Echocardiography showed severe paravalvular aortic regurgitation below the valve stent. Patient 1 developed severe aortic paravalvular leakage and periaortic pseudoaneurysm. Echocardiography showed severe paravalvular aortic regurgitation below the valve stent and thickened, non-homogeneous perivalvular area mimicking aortic root abscess. Patient 20 developed aortic mechanical valve dehiscence with moderate aortic paravalvular leakage and coronary-graft anastmotic leakage.

Discussion
BD is an inflammatory disorder of unknown aetiology showing diverse

Table IV. Follow-up data for patients who developed post-operative complications after the first operation.

Case	Age/sex	Preoperative echocardiographic findings	Operation	Complication	Postoperative echocardiographic findings	Time of postoperative complications	Diagnosis
1	25/M	Severe AR An echo-free space mimicking aortic root abscess	Bentall	APVL	Severe aortic paravalvular leakage and periaortic pseudoaneurysm	1 months after operation	Post-operative diagnosis
5	31/M	Severe AR Prolapse of no aortic valve	Bentall	APVL	Aortic mechanical valve dehiscence with severe aortic paravalvular leakage	3 months after operation	Post-operative diagnosis
6	42/M	Severe AR Prolapse of no coronary valve Vegetation-like mobile lesions of none coronary valve	AVR	APVL	Severe aortic paravalvular leakage	4 months after operation	Post-operative diagnosis
8	38/M	Severe AR An echo-free space mimicking aortic root abscess Severe MR	Bentall, MVR	APVL MPVL Left ventricular-right atrial and right ventricular shunt	Aortic mechanical valve dehiscence with Severe aortic paravalvular leakage Moderate mitral paravalvular leakage Left ventricular- right atrial and right ventricular shunt	3 months after operation	Pre-operative diagnosis
18	51/M	Severe AR Prolapse of no aortic valve Moderate MR Moderate MR	AVR, MVR, TAP	APVL	Aortic mechanical valve dehiscence with severe aortic paravalvular leakage	5 months after operation	Pre-operative diagnosis
19	32/M	Severe AR Prolapse of left aortic valve Moderate MR Moderate TR	AVR, MAP, TAP	APVL	Aortic mechanical valve dehiscence with severe aortic paravalvular leakage	1 months after operation	Post-operative diagnosis
20	25/M	Severe AR Vegetation-like mobile lesions of right aortic valve	Bentall	coronary-graft anastmotic leakage	Aortic mechanical valve dehiscence with moderate aortic paravalvular leakage coronary-graft anastmotic leakage	1 months after operation	Post-operative diagnosis
24	21/M	Severe AR Prolapse of no coronary valve An echo-free space mimicking aortic root abscess	AVR	APVL	Severe aortic paravalvular leakage	2 months after operation	Post-operative diagnosis

AR: aortic regurgitation; MR: mitral regurgitation; AVR: aortic valve replacemen; MVR: mitral valve replacement; MAP: mitral annuloplasty; TAP: tricuspid annuloplasty; VSDR: ventricular septal defect repair; APVL: aortic paravalvular leakage; MPVL: mitral paravalvular leakage

clinical presentations. It is believed cardiac involvement is one of the most severe complications in patients with BD, despite its sporadic occurrence (12). A timely diagnosis is critical for the proper treatment of this serious disease, which often requires surgical interventions. In our study, cardiac involvement in BD was pre-operatively diagnosed by clinicians in 20 patients, accounting for 76.9% of the 26 patients. 6 patients (23.1%) missed or misdiagnosed clinically. It is related that there is no specific diagnostic test for BD, and diagnosis is usually made by a range of clinical finding and the fulfillment of criteria, which are intrinsically obscure. The problem is that clinical presentations of BD may vary widely among individuals and ethnic groups. Diagnostic presentations may be incomplete to meet the criteria at the time of admission or may be overlooked by physicians who are not familiar with BD. Transthoracic echocardiographic examination is the best first choice in the evaluation of potential cardiovascular involvement by BD. We have here presented echocardiographic features and post-operative complications of this uncommon disease. Echocardiography could be useful for the differential diagnosis of cardiac involvement in BD before surgery.

AR is the most important echocardiographic presentation of cardiac BD (5,

8, 9, 11). In our study, 22 of 26 patients (84.6%) were diagnosed with moderate to severe AR. Echocardiographic findings of aortic valve prolapse with marked thinning and redundancy of aortic leaflets, with or without mobile masses and/or echo free space within the annulus, may be pathognomonic of BD (13, 14). It is worth noting that this unusual prolapse with aortic cusp thinning and redundancy are not seen in other diseases. Our study found 16 patients with this unusual echocardiographic findings of aortic valve prolapse, accounting for 61.5% of all cases. The aetiology of valve prolapse in this disorder can be attributed to systemic vasculitis and tissue derangement. Our histologic findings supported both valvulitis and aortitis, such as valvular tissue hyperplasia and myxoid degeneration, perivascular infiltration of lymphocytes in adventitia and vasa vasorum, focal medial necrosis, chronic active inflammation (15).

It should be noted that aortic regurgitation due to BD can frequently be misdiagnosed as infective endocarditis, because of the presence of vegetation-like mobile lesions and an echo free space mimicking aortic root abscess in the echocardiographic evaluation (12, 16). According to our study, 10 patients with vegetation-like mobile lesions or an echo free space were all misdiagnosed as infective endocarditis. Echocardiographic diagnosis likely gives wrong information to the cardiac surgeon. But multiple blood of these patients cultures were negative. The causes of misdiagnosis include that on transthoracic echocardiography, mobile masses noted on valve leaflets are indistinguishable from valvular vegetations, and the echo-free spaces within the annulus and/or ventricular septum are consistent with extension of an infectious process and a root abscess. Furthermore, in patients with BD, mild fever and elevations of acute phase reactants overlap with infective endocarditis, which makes the differential diagnosis even more difficult. Echocardiographic diagnosis likely gives wrong information to cardiac surgeons. Therefore, when echocardiographers suspect infective endocarditis in a patients with an underlying valvular pathology of AR, he or she should carefully ask about the medical history and clinical symptoms of the patient, in order to consider the diagnostic clues of BD.

The surgical treatment of cardiovascular disorders of BD presents many difficulties. The incidence of cardiovascular complications in BD has been reported to be about 30%, and these complications appear to be the main cause of death (8). In cardiovascular lesions caused by systemic inflammatory diseases, it is crucial to reduce inflammation pre- and post-operatively, to reinforce the suture line, and to carefully select the operative procedures. In our study surgical intervention was performed in all patients. The cardiovascular operations that were performed in BD were valve, aorta and pulmonary artery procedures. Post-operative follow-up revealed that complications occurred in 8 out of the 26 patients (30.7%). We found that complications occurred in 6 patients diagnosed post-operatively and in 2 patients diagnosed pre-operatively. The high rate of prosthetic valve detachment after aortic valve replacement is one of the most common and serious consequences of aortic regurgitation in BD, which results in severe aortic annular destruction, presenting a big challenge to cardiac surgeons. In our study the low incidence of complications of BD patients diagnosed pre-operatively may be due to pre- and post-operative steroid and immunosuppressive therapy, suppressing the progression of the inflammatory disease. Recent literature showed delaying surgery in cases with inactive phase inflammation, and initiating immunosuppressive therapy before and after surgery has been recommended (14, 17). In addition, Song (12) found that outcomes associated with each surgical procedure were critically dependent on the lesion severity of cardiac BD in individual patients. Our study found in 5 of the 8 patients with surgical complications (62.5%) the presence of vegetation-like mobile lesions or an echo free space mimicking aortic root abscess. It is indicated that the lesion severity may also be related to the post-operative complications.

Conclusions

Echocardiography has a specific value in the evaluation of pre-operative cardiac involvement and post-operative complications of BD patients. The most common echocardiographic features are severe aortic regurgitation with prolapse of aortic cusps, vegetation-like mobile lesions, an echo-free space mimicking aortic root abscess or aortic aneurysm formation. With particular attention to young and middle-aged male patients with history of recurrent oral aphthosis, genital aphthosis or ocular lesions, echocardiographers observing the above echocardiographic findings should bear in mind the possibility of BD. Accurate pre-operative diagnosis of BD is beneficial to the choice of immunosuppressive therapy before and after surgery, which is likely to reduce post-operative complications especially for patients with severe lesions.

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