

Cardiac complication spectrum of Behçet disease in Tunisia: A 10-case series: Clinical and therapeutic approach

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Abstract

Introduction:

Cardiac involvement (CI), although rare, remains one of the most severe complications of Behçet Disease (BD).

Objective

to investigate the frequency and spectrum of cardiac involvement in BD and to assess the clinical and imaging features, treatment, and outcomes.

Methods

We retrospectively retrieved the medical records of patients with CI among 220 BD patients admitted to the internal medicine department between 2006 and 2016 who fulfilled the International Study Group diagnostic criteria for the classification of BD.

Results

Ten patients were eligible for the study with a sex ratio (male/female) of 8/10. Three cases had 2 isolated episodes of cardiac BD. The mean age when diagnosing the first cardiac episode was 37,3-year-old. The different types of CI were: coronary artery disease (5/10), intracardiac thrombus (4/10) myocarditis (1/10), pericarditis (1/10), myocardial fibrosis (1/10). Vascular involvement was associated to CI in 5 cases (50%). The main symptoms were chest pain (80%), fever (60%), dyspnea (50%), cough (10%) and hemoptysis (10%). The laboratory tests revealed increased inflammatory markers in 5 patients. Medical treatment was based on colchicine and corticosteroid in all patients (100%), anticoagulants in 8 patients (80%), Cyclophosphamide followed by Azathioprine in 9 patients (90%), Azathioprine monotherapy was started in one patient (10%). Antiplatelet and anti-ischemic therapy in 5 patients who had coronary artery disease. The evolution was favorable in 9 cases and marked by severe heart failure and the death of one patient.

Conclusion

CI despite its rarity, remains an important feature of BD due to the increased risk of mortality and morbidity. Thus, early screening and detection are paramount. Also, imaging has been of great contribution to diagnose such complications and hence indicate the adequate treatment, including immunosuppressant agents.

Background

Behçet's Disease (BD) is a systemic inflammatory vasculitis of unknown etiology with a remitting relapsing course. It is more common and (often more severe) along the historic silk road which extends

from Eastern Asia to the Mediterranean. Mean age of onset is between 20 and 40-year-old [1, 2]. The prevalence in males and females varies according to the region. In the Middle Eastern and Mediterranean countries, the incidence is higher in males, whereas it is more frequent in females in Northern Europe and the United State [3, 4].

BD is characterized by recurrent episodes of oral and genital aphthous ulcers, cutaneous and ocular lesions as well as other manifestations, such as gastrointestinal, musculoskeletal, neurological and cardiovascular events [5, 6]. Vascular involvement is among the main features of this disorder and is reported in more than 40% of BD patients affecting both arteries and veins of different calibers. However, cardiac lesions including (pericarditis, intracardiac thrombi, active valvulitis, myocardial fibrosis, etc.) has been reported only sporadically [7].

Data about incidence, nature, severity and management of such cardiac manifestations among the Tunisian and North African region is not well established. The aim of this study is to investigate the prevalence, the clinical spectrum, imaging features, treatment, and outcome of BD with cardiac involvement (CI).

Methods

We retrospectively studied the medical records of 220 BD patients admitted at the internal medicine department of Fattouma Bourguiba's University Hospital between 2006 and 2016. All of our patients fulfilled the International Study Group (ISG) for Behçet's disease criteria [2].

Only cases with cardiac involvement were selected for this study. Cardiac lesions included pericarditis, myocarditis, endomyocardial fibrosis, intracardiac thrombus, myocardial infarction, coronary thrombosis or aneurysm. Screening for cardiac complication was performed only in symptomatic patients.

Cardiac Involvement was mainly diagnosed based on clinical grounds and imaging techniques including echocardiography, chest computed tomography, cardiac magnetic resonance imaging and coronary angiography. Pathology was also of a great contribution to nail down some specific manifestations.

Baseline demographic and thorough clinical data were collected from respective standard hospitalization documentation and medical records.

Results

Patient characteristics

Among 220 patients with BD only 10 were found to have CI, (4,5% of all patients) with a mean age of 37.3-year-old (range 20–49). Three of them had 2 episodes of cardiac BD. Sex-ratio (male/female) was 8/10.

CI was the presenting symptom of BD in three cases. In fact, the diagnosis was established retrospectively one year after finding an intracardiac thrombus (ICT) in a patient having a congenital heart disease. Also, coronary artery disease was the first manifestation of BD in 2 other patients. CI appeared during the course of the disease in the other 7 cases and it was up to 2.3 (range 1–9) years after the onset of BD.

The demographic variables and diagnostic criteria are shown in Table 1.

Table 1
Demographic characteristics and criteria for Behçet's disease.

Parameters	N (%)
Gender (male/female)	8/2 (80)
Mean Time since the diagnosis of CI (years)	2.3
Recurrent oral ulcer (%)	10 (100)
Genital ulcer (%)	7 (70)
Skin lesions (%)	6 (60)
Eye involvement (%)	5 (50)
Positive pathergy test (%)	3(30)
Articular involvement	3 (30)
Vascular involvement	5 (50)

Vascular involvement whether arterial or venous was found in 5 patients (50%) with 10 manifestations in total: several cases had deep venous thrombosis, including superior/ inferior vena cava thrombosis in two patients, lower limb in one. On the other hand, arterial involvement varied from pulmonary aneurysm (n = 1) to pulmonary embolism (n = 2) and less frequently the disease led to occlusion of some systemic arteries: Right Brachiocephalic artery (n = 2), cerebral artery thrombosis in one patient (n = 1) and superior mesenteric artery aneurysm (n = 1).

Clinical features

In this section, 13 events of CI encompassing 10 patients will be analyzed. The different types of CI were as follow: coronary artery disease (CAD) (5/10) (one patient presented two episodes of CAD), intra-cardiac thrombus (ICT) (4/10), myocarditis (1/10), pericarditis (1/10), myocardial fibrosis with endocarditis (1/10).

The main symptoms were chest pain (80%), tachycardia (60%), fever (60%) and dyspnea (50%). One ICT case associated to a pulmonary embolism presented with symptoms of cough (10%) and hemoptysis (10%), while in another (10%), syncope was the presenting sign.

On physical exam, we found a cardiac murmur in 3 patients (30%), superior vena cava syndrome in one (10%). Two patients presented with heart failure symptoms (20%), one of them had a history of congenital heart disease (tri-atrial heart).

Electrocardiography was performed in all patients. It showed left ventricle enlargement features in 2 cases (20%), an incomplete right bundle-branch block in one case (10%) and premature ventricular complexes in another (10%). In the acute setting of acute coronary syndrome 4 patients exhibited Non ST-Elevation myocardial infarction (NSTEMI) involvement (in the lateral, posterior and inferior leads (2 patients)) whereas another displayed a posterior ST-Elevation myocardial infarction (STEMI).

Laboratory findings

Laboratory tests revealed increased inflammatory markers in 5 cases (50%), the average rate of the Erythrocyte Sedimentation Rate and C-Reactive Protein were respectively 57.9 mm/h (5–111) and 47.5 mg/l (6–204). Troponin level was significantly raised in 5 patients (50%). Bacterial cultures conducted in patients who had fever were all negative. Coagulation profile was performed in 5 patients, 4 of those had ICT with a lab workup that came back negative, 1 patient with fibrosing myocarditis showed positive antiphospholipid antibodies (Anti-cardiolipin IgM at 100UI and IgG at 7 UI) along with normal coagulation studies. Plasmatic Homocysteine level was raised in 1 patient (27 μ mol/l). Human leukocyte antigen (HLA B 51) tested in all patients was positive in five (50%).

Imaging features

Echocardiography

Transthoracic echocardiography was conducted in 10 patients. It was coupled with trans-esophageal echocardiography in 4, mainly those who had ICT and was performed either for the differential diagnosis or to precisely assess thrombi in the left atrium. In fact, only one patient had a left atrium thrombus in the setting of a congenital heart disease (Cor-Triatriatum), the remaining ones (3) had right atrium and right ventricular thrombi (Fig. 1). Among other echocardiographic finding, we found a left ventricle hypokinesis in patient number 1 (Table 2) that was eventually diagnosed with a myocarditis and a moderate pericardial effusion (10 mm anteriorly, 15 mm posteriorly) unfolding a pericarditis in patient number 3. Coronary artery disease patients were consistently assessed with a cardiac echocardiography displaying pulmonary artery hypertension in patient number 2 and 8 and normal findings in the remaining ones. Furthermore, patient number 7 who had the worst prognosis was found with multiple vegetations revealing initially infective endocarditis however he was subsequently found with endomyocardial fibrosis on histopathological specimen examination.

Table 2
 Characteristics of lesions, treatment and outcome for BD patients with cardiac involvement

Case	Gender	Cardiac lesion	Vascular involvement	Treatment	Follow up (years)	Outcome
1	Male	Myocarditis	No associated	Colchicine CS, IS, Antiplatelet	2	complete resolution
2	Male	Cardiac thrombosis	Inferior vena cava thrombus, pulmonary embolism	IS, Colchicine, CS, AC	10	Control echocardiography (5 months): resolution of the thrombus
		coronary stenosis		Colchicine, CS, AC, IS, PTCA	4	Clinically stable
3	Male	Pericarditis	Pulmonary embolism and, aneurysm, Cerebral thrombosis,	NSAIDs	1	Resolution without recurrence
		cardiac thrombosis	Superior vena cava thrombus, occlusion of the right Brachiocephalic artery	AC, Colchicine CS, IS	13	complete resolution
4	Female	cardiac thrombosis	No associated	AC, CS, IS, Colchicine	10	Clinically stable
5	Male	coronary aneurysm	No associated	CS, IS Colchicine	2	Stabilization for 2 years, then he presented a second acute coronary syndrome
		coronary stenosis		CS, PTCA, AC, IS, Colchicine,	13	Clinically stable

Antibiotics (ATB) Corticosteroids (CS), Immunosuppressant (IS), Anticoagulant (AC), Non-Steroid Anti-Inflammatory drugs (NSAIDs), Deep Venous Thrombosis (DVT), Percutaneous Transluminal Coronary Angioplasty (PTCA), Coronary Artery Bypass Grafting (CABG)

Case	Gender	Cardiac lesion	Vascular involvement	Treatment	Follow up (years)	Outcome
6	Female	cardiac thrombosis	DVT (lower limb)	AC, CS, IS Colchicine	3	Clinically stable
7	Male	Endomyocardial fibrosis	Superior Mesenteric artery aneurysm	ATB, CS, IS AC, Antiplatelet Colchicine,	1	Death
8	Male	coronary stenosis	No associated	CS, IS Colchicine PTCA	2	Clinically stable
9	Male	coronary stenosis	No associated	CS, IS Colchicine PTCA	16	Clinically stable
10	Male	coronary stenosis and aneurysm	occlusion of the right Brachiocephalic artery	CS, IS Colchicine CABG	2	Clinically stable
Antibiotics (ATB) Corticosteroids (CS), Immunosuppressant (IS), Anticoagulant (AC), Non-Steroid Anti-Inflammatory drugs (NSAIDs), Deep Venous Thrombosis (DVT), Percutaneous Transluminal Coronary Angioplasty (PTCA), Coronary Artery Bypass Grafting (CABG)						

Computed Tomography

Was conducted in 4 patients. It confirmed the diagnosis of ICT. Furthermore, it was the tool used to scrutinize the vascular system and hence detect any associated lesion.

Computed tomography revealed a right atrial pedunculated mass in accordance with a thrombus in patient number 2. However, it also showed a partial occlusion of the inferior vena cava and thrombosis of the left lobar pulmonary artery with many pulmonary infarcts. Two other patients (number 3 and 4) were found with a double ICT (right atrium and ventricle). In case number 6, Computed tomography exhibited the left atrial intra-cardiac thrombus described in Ultrasound but it also revealed vascular involvement (a partial obstruction of the inferior vena cava as well a pulmonary artery thrombosis and aneurysms).

Cardiac Magnetic Resonance Imaging

Cardiac Magnetic Resonance Imaging was performed in one patient having myocarditis. It showed a myocardial signal intensity increase in T2-weighted images in the antero-lateral and inferior segments of the left ventricle (Fig. 2).

Coronary angiography

This was conducted in 5 patients who had evidence of CAD. Four of them had an NSTEMI and only one had a lateral STEMI, the latter (patient number 9) was found with a tight stenosis of the left circumflex artery. Patient number 5 was hospitalized twice for CAD: an unstable angina pectoris (1st hospitalization) revealed a middle right coronary artery (segment II) aneurysm (Fig. 3). Two years later, he was hospitalized for an inferior NSTEMI revealing an 80% occlusion of the right coronary artery.

Moreover, patient number 10 was found with a tight stenosis of the main left coronary artery and a large aneurysm of the Left anterior descending artery in the context of a lateral NSTEMI. The remaining two patients (number 2 and 8) both benefited also from primary transluminal coronary angioplasty in the setting of anterior and inferior NSTEMI respectively.

Histopathology

One patient (number 7) had an infective endocarditis following a superior mesenteric artery aneurysm surgery. which was initially treated with antibiotics, then by a valvular replacement. Histologic examination of the specimen showed an endomyocardial fibrosis with a parietal thrombus.

Treatment

Medical treatment was based on colchicine (1 mg/day) associated to corticosteroids in all cases consisting of 3 daily intravenous pulses of methylprednisolone (15 mg/kg/day) followed by oral prednisone (1 mg/kg daily) gradually tapered over 6 months. Six-month pulses of cyclophosphamide followed by azathioprine were administered in 9 cases (90%). Three patients (30%) had a second 6 month course of Cyclophosphamide due to the recurrence of their CI. Azathioprine monotherapy was started in one patient (10%). Oral anticoagulation treatment was used in 8 cases (80%). Five patients (50%) did benefit from a double antiplatelet therapy [Aspirin-Clopidogrel] in the setting of an acute coronary syndrome. Percutaneous transluminal coronary angioplasty was conducted in 4 patients (20%) and it was successful in two and failed in others. One patient (10%) had a tight stenosis of the main left coronary artery and a large aneurysm of the left anterior descending artery underwent a double coronary artery bypass grafting procedure. Antibiotic therapy was indicated in only 1 patient (30%). Patient number three (10%) with pericarditis received non-steroid anti-inflammatory drugs.

Surgical valvular replacement was indicated in patient number 7 who had an infective endocarditis following a superior mesenteric artery aneurysm surgery.

Outcomes

After treatment, the outcome was marked by severe heart failure and the death of one patient (10%) with an endomyocardial fibrosis. Furthermore, 2 patients had a relapse of their cardiac involvement; the rest of patients had a favorable evolution. They are all still being monitored with regular clinical and laboratory follow up (Table 2).

Discussion

Behçet disease is a chronic inflammatory disease of unknown origin that might have been described by Hippocrates [8] but it was brought to the attention of the modern medical community by the Turkish dermatologist Hulusi Behçet in 1937 [6, 9].

This disease is characterized by a relapsing course of oral aphtae and multiple systemic manifestation including genital aphtae, ocular and neurologic disease, respiratory, gastrointestinal and cardio-vascular manifestations [3, 4, 10]. Although the CI remains rare in most cross-sectional studies, its prognostic influence on the course of BD and its insidious onset should be addressed. Thus, this paper is among the first to focus on cardiac manifestation in the North African region [11].

Behçet disease criteria

There is no pathognomonic test to diagnose BD. It is best assessed based on clinical grounds in the context of recurrent aphthous ulcerations along with systemic manifestations. As a result, we used the diagnostic criteria published by the *International Study Group* in 1990 [12]. In 2006, *The International Team for the Revision of the International Criteria for Behçet's Disease* had established new criteria in an effort to improve sensitivity; therefore, vascular involvement was added while oral aphthae were no more mandatory for diagnosis [13–15]. Though, the ISG criteria remain the most widely and well-accepted criteria that exhibit relatively decent sensitivity and specificity applicable all across the world [15, 16]

Cardiac disease was the first manifestation in nearly 30% of BD cases with CI in large cohort studies [11, 17]. Accordingly, the diagnosis of cardio-BD should be considered even in cases when the classical criteria are absent, especially in young male patients residing at the Silk Road route. In these cases, a detailed analysis of the heart and large vessel structures are recommended by imagery and an adapted follow-up should be implemented [2].

Epidemiology

Cardiac involvement is a rare finding in BD ranging between 0.13–16.5% of patients according to previous studies. This frequency varies depending on the ethnic groups and geographic parameters [1–3, 17–23] (Table 3).

Table 3
frequency of cardiac involvement in Behçet Disease in the literature

Author (country)	Year	Number of the patients with BD	Cardiac involvement frequency
Lakhanpal(Japan) [19]	1985	170	16.5%
Assaad-Khalili(Egypt) [24]	1993	350	15%
Gurler (Turkey) [21]	1997	2147	0.13%
B'chir Hamzaoui (Tunisia) [22]	2006	519	2%
Geri (France) [17]	2012	807	6%
Zhang (China) [23]	2013	334	8,1%
Wang(China)[3]	2016	626	1.9%
Our study	2020	220	4.54%

CI occurred mostly in young males in our study. Likewise, **Wang** et al. reported [3] that BD patients with ICT had a sex-ratio of 9/12 (75% males) with a mean age of 33.5-year-old. According to these observations, CI tends to occur more often in young male adults.

The frequency of different types of CI varies from one study to another. This is among the very first study with a high incidence of coronary artery involvement with 50% of patients affected. In addition to that, 40% had ICT and only sporadically did we find other lesions (myocarditis, pericarditis, endomyocardial fibrosis, etc.). In contrast, in **Geri** et al. study, 807 French BD cases were included with 48 patients having CI; depicting 38% as pericarditis, 26% as endocarditis, 19% as ICT, 17% as myocardial infarcts, 7% with endomyocardial fibrosis, and 2% with myocardial aneurysm [17].

Pathophysiology, histopathology

There is no known underlying cause of BD. As any autoimmune disease the disorder might be due to an aberrant immune response in genetically predisposed individuals. Hence the positive correlation of HLA B51 with BD activity and severity [25]. This abnormal immune reaction might be triggered by exposure to some viral or bacterial epitopes [26].

Many clinical manifestations including cardiovascular involvement are thought to be due to vasculitis [27]. In fact, activated neutrophils cause excessive oxidative stress through an increased level of free radicals like superoxide anions and lysosomal enzymes. This happens along with a disequilibrium of scavenging enzymes which eventually leads to destructive effects [15]. Indeed, vasorum occlusion and transmural necrosis in the walls of the large muscular arteries ensues leading to deterioration of blood flow and then degeneration of vessel wall [28, 29].

Thromboembolism mainly triggered by endothelial dysfunction is also a characteristic finding in BD, so endothelium-dependent flow-mediated dilation is diminished causing therefore an increase in vascular inflammation. Furthermore, the associated thrombin and fibrin release and decreased fibrinolysis [28, 30] will eventually lead to heart and vessel lesions [31, 32].

The dysfunction of autonomic nervous system has also been suggested as an etiology especially in the cases of silent myocardial infarction [33].

The role of antiphospholipid antibodies, especially anti-cardiolipin, is still controversial in BD [34]. In some studies, these antibodies have been suggested to have a causative role in the intra-cardiac thrombi formation e.g. in **Wang** et al. study, among 7 BD patients with ICT, lupus anticoagulant was detected in 2 of them [3] which is in agreement with our findings as anti-cardiolipin antibody was positive in one patient. hyperhomocysteinemia has also been advocated in some papers as being a predictor of BD activity; even more it might contribute to the pathogenesis of the disease which could explain its positivity in our series [18] .

Histopathology

Classically, BD related lesions show a necrotizing leukocytoclastic obliterative perivasculitis associated with a venous thrombosis and a lymphocytic infiltration of capillaries, veins, and arteries of different calibers. When a full-blown vasculitis is present, we might find fibrinoid necrosis of vessel wall, endothelial swelling and extravasation of erythrocytes[1, 13, 27] .

Endomyocardial fibrosis is a complication rarely seen in BD exhibited by one of our patients. The typical pathologic findings include a dense fibrous tissue with neovessels, mononuclear and polymorphonuclear infiltrates, along with calcified spots [17, 34].

Clinical features

Diagnosis time lag

Cardiac involvement can be the cardinal manifestation of BD or can appear after the diagnosis by months or even years [3, 17, 35–37].

In our study, CI was the presenting manifestation of the disease in three cases (30%), which is consistent with previous results, as in **Geri** et al. findings [17], where they reported 32.7% of patients having primarily cardiac BD. This involvement is often silent; it could be screened by imaging i.e. angiography or holter monitoring in asymptomatic patients when the diagnosis of BD is made [33, 38]. In the symptomatic patients, clinical features differ according to the type of the involvement.

Coronary artery disease

Coronary artery involvement in BD is extremely uncommon, thus the importance of our study to highlight the target population characteristics and the prognosis of such involvement. As previously described, this

affects mainly young male patients without cardiovascular risk factors living across the ancient silk road such as Turkey, Middle East, Mediterranean basin and other Asian countries [39, 40]. This involvement is exceptionally rare due to the wide presenting symptoms and perhaps the silent form that goes under diagnosed. As a matter of fact, according to **Turkolmez** et al. study [41] silent myocardial ischemia has been found in 19,5% of BD patients compared to 2.9% of sex- and age matched of healthy control group; other symptoms include angina pectoris or congestive heart failure [11, 17, 37, 42, 43].

Usually coronary artery disease (CAD) is a complication occurring in patients already diagnosed with BD, however as showed by two cases in our series it can be the initial presentation revealing the disease [44] especially in the Mediterranean basin as oral aphtosis is a common finding not always pointing to BD. Lesions affecting coronary arteries include stenosis, occlusion, in-stent stenosis, aneurysm and pseudo aneurysm [37, 43, 45, 46]. The course of CAD in young patients can also be a feature unfolding the diagnosis, especially if we find repeated in-stent stenosis, aggressive progress, and elevated inflammation markers. Recently, **Ma** et al [46] reported a middle aged male, in whom BD was revealed by an abdominal aorta pseudo aneurysm. This patient had coronary artery lesions 10 years before the diagnosis of BD with repeated in-stent bypass graft restenosis despite a good control of cardiovascular risk factors and an intensive medical treatment [45, 46]. Hence, the urge of developing new screening methods for an early diagnosis.

Management of CAD in the context of BD can be very challenging since the guidelines are not yet well established, for example anticoagulant and thrombolytic may precipitate bleeding in aneurysms [47] and corticoid pulses can curtail the heart healing process and hence rendering it more prone to rupture [39, 48]. In addition, mechanical manipulation of the coronary vessels through surgery or angioplasty while the vasculitis is still ongoing is considered very risky and can worsen the prognosis even more [49]. Therefore, patients must receive adequate medical therapy to minimize the vasculitis and to improve outcomes [50]. However, despite the therapeutic burden of the disease, classic measures are still implemented with an early start of medical therapy and an optimal control of cardiovascular risk factors [2, 45]. The cornerstone of CAD treatment in the setting of BD remains the early implementation of anti-inflammatory agents as highlighted in **Ma** et al. study [46]. Consequently, non-use of corticosteroids and immunosuppressant exposes the patient to the extension and the recurrence of the complication.

Intracardiac thrombus

Compared to venous thrombi, ICTs are relatively uncommon in BD.

According to our findings, only 1.8% of the original BD pool were affected which is consistent with the prevalence in **Wang** et al. study [3], noted in 1.9% among 626 BD patients. ICT was the second cardiac complication in our series (40% of cases) and this can be explained by the geographic influence: The Mediterranean basin being an endemic area [11]. Usually, it occurs in male aged < 40-year-old without adequate immunosuppressive therapy within 10 years of the diagnosis [3], but It might also be the presenting sign of BD as observed in patient number 6.

In agreement to previous studies [1, 37], ICTs involved the right heart chambers more often (3 vs 1 left atrial thrombus) than the left, perhaps because some are extended thrombi from the vena cava and also because the lower pressure in the right heart predisposes for stasis of blood flow, one of Virchow triad criteria. Furthermore, there is a predilection to involve ventricles more than atriums [4, 9] but the reason is still unclear [10, 51]

Clinically, the main symptoms are palpitation, hemoptysis, cough and dyspnea. Also, fever and heart failure symptoms might be present [1, 39]. ICT can also be revealed by a pulmonary embolism as seen in one of our patients, or embolic strokes caused by emboli passing through the patent foramen ovale. Sometimes patients are asymptomatic and ICT is then diagnosed only by an ultrasound screening [3, 18]. Considering differential diagnosis, myxoma is among the first, however in the context of BD we should primarily suspect an ICT in front of a right ventricular mass compared to the frequent left atrial location of cardiac tumors [9, 52]. For that reason, imaging is a major tool to narrow down the diagnosis. In addition, right heart chamber thrombus is highly specific for BD thus, the diagnosis should be on the differential even though other symptoms are absent [9, 10]. ICT are also often reported to be associated with deep vein thrombosis and pulmonary artery aneurysms [1, 4, 9, 53].

Until now no guidelines or large cohort with evidence based medicine have been proposing a standard treatment, in fact it mainly depends on the discretion of physicians and habits of every treating center [39]. What is primarily used is a combination of anticoagulants and immunosuppressive drugs and that's what we opted for in our tertiary referral center. Other hospitals, also use remotely thrombolytics when the clot is mobile [2].

Some studies suggest that unlike the common thrombotic diseases, BD thrombosis is positively correlated with the extent of vasculitis and hence the rationale favoring the use of immunosuppressive drugs [3] .

When associated to a pulmonary arterial aneurysm as in one of our patients, ICT must be treated with an intensive immunosuppressive treatment. However, anticoagulant and antithrombotic therapy should be given cautiously due to the risk of bleeding. Trans catheter embolectomy could be beneficial in this case [1–4]. Besides, the “European League Against Rheumatism” recommends the use of cyclophosphamide in the cases of ICT and pulmonary arterial aneurysm [54].

Severe ICT i.e. causing heart failure requires surgical excision, but an isolate surgery does not lead to complete resolution, it must be associated to immunosuppressive drugs, steroids, and warfarin [1, 52].

Pericardial involvement

In contrast to our study, pericardial involvement has been reported as the most common manifestation representing respectively 40% and 38.5% of CI in **Wechsler** et al. and **Geri** et al. studies [17, 20]. This complication can also be the cardinal presentation of BD and can be recurrent but rarely does it lead to further complications such as constrictive pericarditis [17].

Pericardial effusion manifests with a stabbing chest pain, fever and dyspnea. An asymptomatic pericardial effusion can be detected by electrocardiographic abnormalities or a systematic echocardiography [2, 43, 55, 56].

Moderate pericarditis, can be treated with non-steroid anti-inflammatory drugs and less frequently immunosuppressive agents are indicated [4]. Emergency pericardiocentesis is required if the pericarditis is complicated by a tamponade [2]. Moreover, colchicine, indicated in all cases of BD, has been reported as an efficient treatment of pericarditis whatever its etiology, even when it is recurrent [57]. Our patient had initially a favorable evolution with a therapy combining Colchicine and non-steroid anti-inflammatory drugs.

Endocardial involvement

Endocardial involvement manifests mainly as a valvular dysfunction or more rarely as endomyocardial fibrosis. It can also be misdiagnosed as infective endocarditis, accordingly if the presentation in incomplete and echocardiographic findings are present Major Duke criteria can be met resulting eventually in a delayed diagnosis, a worse prognosis and sometimes complicated surgeries[11, 39].

For discrimination purposes endocarditis and vasculitis in BD are recurrent and acute rather than persistent and chronic. One of our patients had a valvular replacement and antibiotic therapy after being diagnosed first with infective endocarditis as a complication of a superior mesenteric artery aneurysm surgery. Then, he was hospitalized a second time for a severe heart failure due to endomyocardial fibrosis. The course was fatal and culminated with the death of the patient. This could again be due to the confounding diagnostic dilemma of infective endocarditis. That's why in valvular pathology, the diagnosis of infectious endocarditis is generally excluded by the inefficacy of antibiotics treatment, hence a therapy combining corticosteroids and immunosuppressive agents is then indicated.

As far as valvular involvement is concerned, aortic and mitral valves are the most affected valves [38] indeed aortic valve insufficiency is ranked as the second most common cardiac complication in **Gueri** et al. study [17]. Clinically, valvular lesions can be presented as an isolated acute or subacute manifestation or as a valvular regurgitation diagnosed by echocardiography.

Endomyocardial fibrosis is an exceptional but a severe complication of BD. It is usually presented by right heart failure symptoms and diagnosed during specimen microscopic examination as conducted in our tertiary center. This could be the sequelae of vasculitis involving the myocardium, endocardium, or both, complicated by mural thrombus [17].

For our patient, endomyocardial fibrosis could also be explained by the increased antiphospholipid antibodies that have contributed to the pathogenesis of this complication.

Management of endocardial involvement is controversial, due to the wide differential diagnosis and the frequent absence of all BD criteria. For instance, **Jeong** et al. [58] found that patients operated for aortic regurgitation without considering their underlying BD had a fatal outcome (47.3% mortality rate).

Endomyocardial fibrosis is usually treated with colchicine, immunosuppressive agents [2] however, if it is complicated by heart failure surgical excision can be successful.[59]

Myocardial involvement

isolated myocarditis is rarely reported in BD. It was found in 2 patients among 28 with CI in BD in a Japanese autopsy review [19] and only one case among 52 European patients in **Geri** et al. study [17]. The diagnosis is suspected in front of a patient with symptoms of a heart failure, conduction abnormalities, or kinetic abnormalities in the ultrasound [56, 60].

It seems that myocardial involvement's frequency is underestimated, the prevalence is reported to be more important in the studies where patients underwent a systematic imaging screening exam: an echocardiography or a scintigraphy [11, 18].

Treatment is mainly based upon the management of heart failure, and treatment of arrhythmias and immunosuppressive therapy should always be implemented when BD is highly suspected.

Associated systemic vascular involvements

Our findings are in accordance with previous papers, as patients with cardiac involvement had frequently affected vessels [3]. This might be explained by similar pathophysiologic processes that are positively correlated with inflammation and disease activity [3, 54]. Behçet disease is remarkable for its ability to involve different calibers of blood vessels, on both the venous and arterial sides of the circulation [1–4, 23, 38].

According to previous studies, the venous system is usually the most affected [54], 50% of our patients had venous lesions. This involvement was frequently associated to ICT. Indeed, **Wang** et al. reported that 75% of patients with ICT had inferior or superior vena cava thrombi, hence the assumption that right heart ICTs prevalence might be due to extension of venous thrombi [3].

Arterial involvement, is also common in BD patients with heart complications and is usually expressed by aneurysms, pseudo aneurysms or stenosis [11, 42].

Pulmonary involvement is a systemic involvement frequently associated to cardiac complications especially along ICT [1]. Pulmonary embolism was found in 2 out of 10 patients in our study; Despite being rarely reported in literature because of the strongly adherent tendency of clots in deep veins [46]. This could be explained by the migration of ICTs instead. On the other hand, **Mogulkoc** et al. [37], found that 12 out of 25 patients with ICT (48%) had pulmonary arterial aneurysms (PAA) which are an important cause of massive hemoptysis[11, 42] as seen in one case in our study. As a result, the association between PAA and ICT in BD increases the risk of hemorrhage and especially of hemoptysis by anticoagulant use [60, 61].

Electrocardiography

It is not uncommon to find abnormalities like atrioventricular block during BD. It is reported in 23.1% in **Gao et al.**, and according to the same study prompt management is recommended even with mild conduction disturbance [62, 63]. Also arrhythmia such as paroxysmal atrial tachycardia, complex ventricular arrhythmias, premature ventricular beat, or conduction defects as QT dispersion can be found [11, 55]

Laboratory finding

Laboratory tests typically reveal increased inflammatory markers with a significantly elevated Erythrocyte Sedimentation Rate and C-Reactive Protein, and white blood cell count. These finding could guide the diagnosis of BD in front of cardiac complications without cardiovascular risk factors in a young Mediterranean male [1, 3, 4, 38]. Furthermore, troponin level can be elevated in the case of myocardial ischemia but Pro-BNP value can be raised in several forms of CI [2].

Autoimmune and thrombophilia screening including antiphospholipid antibodies (anti-cardiolipin antibody, anti- β_2 glycosidoprotein 1 antibody, and lupus anticoagulant), genetic procoagulant factors (Protein C&S deficiency, Antithrombin deficiency, Prothrombin gene mutation, factor V Leiden mutation) is frequently performed and is usually negative [1, 3, 4]. Nevertheless, it could show positive antiphospholipid antibodies whose correlation with CI is controversial [3, 34]. Human leukocyte antigen (HLA B51), positive in 5 out of 10 patients, is usually screened. Many studies have confirmed the evidence linking HLA-B*51 with susceptibility for BD, but no study has demonstrated its relationship with CI [51, 64].

Imaging features

Echocardiography was performed in all our patients, whether transthoracic or trans-esophageal, is a simple, available and a harmless exam. It contributes to identify early cardiac lesions and to appreciate their severity and extent even in asymptomatic patients [11, 22, 38]. Consequently, echocardiography is often recommended in BD patients by many authors. In the study of **Ulusan et al.** [65], echocardiography was performed in 38 asymptomatic BD patients. It detected aortic valve insufficiency in six and mitral valve insufficiency in three patients. Therefore, Echocardiography remains a paramount tool used not only for CI screening in BD but also for early diagnosis and treatment indications.

Computed tomography can help in detecting ICT showing amorphous, homogeneous, medium and hyperdense mass. It is also a vascular involvement screening tool remotely revealing arterial aneurysms, venous thrombosis or pulmonary embolism [1, 4, 42]. The main drawback of Computed tomography, is that it exposes to radiation and contrast medium complications. It was conducted in 3 of our patients and led to the confirmation of ICT and pointed out to some of the vascular system involvement.

Cardiac magnetic resonance imaging has become an ineluctable exam that identifies and appreciates the extension of CI in BD. This exam is usually indicated in myocarditis or ICT. It aids in having an objective assessment of myocardial inflammation [66]. Cardiac magnetic resonance imaging also detects functional and morphological abnormalities as well as tissue pathology as diagnostic features of

myocarditis. Furthermore, it determines the regional distribution and extent of reversible and irreversible myocardial injury [66]. That's why, Cardiac magnetic resonance imaging was critical in detecting myocarditis in one of our patients. Secondly, it can be a relevant tool in differentiating ICT from a cardiac tumor i.e. myxoma, as thrombus is avascular without contrast uptake [3, 52]. In **Wang** et al. study[3], Cardiac magnetic resonance imaging was performed in four patients with ICT and revealed 3 masses with isointense signal on T1-weighted image and low signal on T2 weighted images, delayed enhancement was depicted in one patient who had organized clots associated with inflammatory cells.

Coronary angiography is the gold standard in the case of CAD as it can identify not only occlusions but also aneurysms which are characteristic findings of BD. These latter could have a saccular or fusiform aspects in angiography [51]. However, if conventional angiography is chosen it is important to be careful with its complications like pseudoaneurysmal formation and infectious risk with femoral puncture. As a result, non-invasive methods such as ultrasonography, magnetic resonance and computerized tomography angiography should be preferred primarily for diagnosis [28].

Treatment

Generally speaking, the aim of the CI in BD's treatment is to alleviate symptoms, and to prevent permanent organ damage by repressing inflammation. That's why, there is no specific treatment, the above treatment options are still based on a low level of evidence.

Consequently, pharmacological agents including colchicine, corticosteroids, immunosuppressive agents (cyclophosphamide, cyclosporine, azathioprine), more rarely tumor necrosis factor- α inhibitors, interventional and surgical treatment are the main options we have [1, 2].

Prognosis

Overall, survival in BD patients with CI is unfavorable as compared with those who don't. Global mortality of BD is estimated at 5.4% in 5 years, and reach 15.4%-20% in such a complication[7, 24, 42]. Better prognosis was found in the cases of an earlier diagnosis especially with the early introduction of anti-inflammatory (immunosuppressants, colchicine) agents that offset the inflammatory burden [2, 17, 42]. Vascular aneurysm rupture is reported to be the most common cause of mortality. Hence, poor prognosis was reported in the case of BD associated to CAD as it can lead to severe coronary aneurysms. Accordingly, 25% of mortality was due to CAD in **Geri** et al study [17]. Also, endomyocardial fibrosis can be fatal in the course of BD [39] leading to a severe heart failure as seen in patient number 7.

Conclusion

Cardiac involvement, despite its rarity in BD, is among the most severe complications.

It is usually present in young male and may affect the three cardiac tunics and the coronary arteries. Echocardiography remains one of the major radiologic exams that can lead to an efficient early screening of asymptomatic patients along the Silk Route pathway. Furthermore, Cardiac Magnetic Resonance

Imaging is also a great tool to highlight some of the complications like myocarditis or ICT. The prognosis of cardiac complications is worse than any other systemic manifestation. Therefore, early administration of colchicine and immunosuppressants agents is paramount and can improve survival rates.

Abbreviations

CI

Cardiac Involvement,

BD

Behçet Disease,

ICT

Intacardiac Thrombus,

CAD

Coronary Artery Disease,

STEMI

ST-Elevation Myocardial Infarction,

NSTEMI

Non ST-Elevation Myocardial Infarction,

ISG

International Study Group.

Declarations

Ethics approval and consent to participate

This study was approved by the institutional committee of Fattouma Bourguiba University hospital. Written inform consent was waived due to the retrospective and observational nature of this study.

Consent for publication

Not applicable.

Availability of data and materials

Datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

ASH conceived this study, ASH and MJ analyzed and interpreted data, and drafted the manuscript. MBB, SD, MH and MK contributed through the acquisition and collection of data. SO, MKH and JS revised the manuscript. All authors read and approved the final manuscript.

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Figures

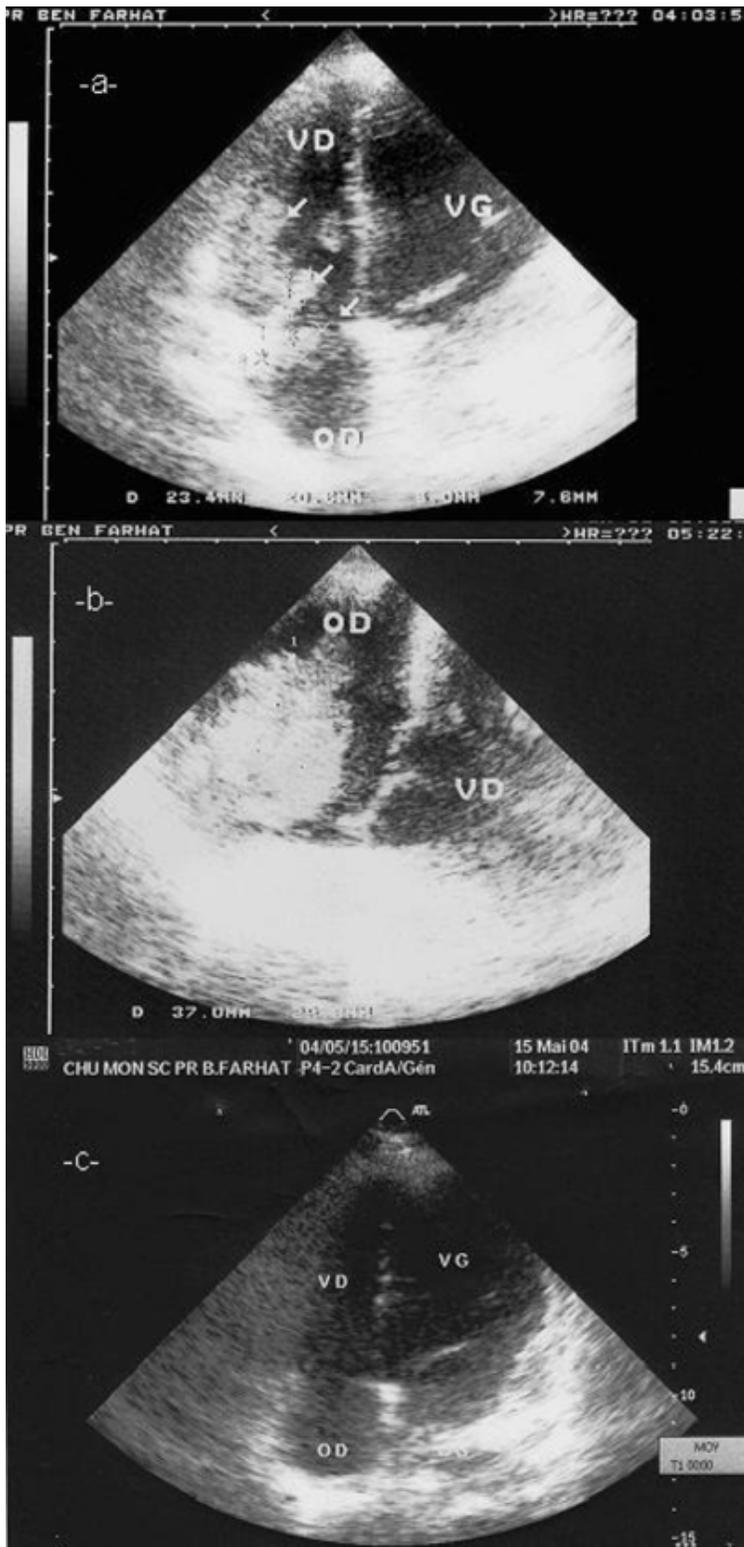


Figure 1

Transthoracic echocardiography in patient number 3: Apical four chamber view (VD: right ventricle, VG: left ventricle, OD: right atrium, OG: left atrium) a) Image of one thrombus in the right atrium, and two thrombi in the right ventricle. b) Trans-esophageal echocardiography exhibiting the right atrium thrombus c) complete resolution of the the thrombi after treatment [67].

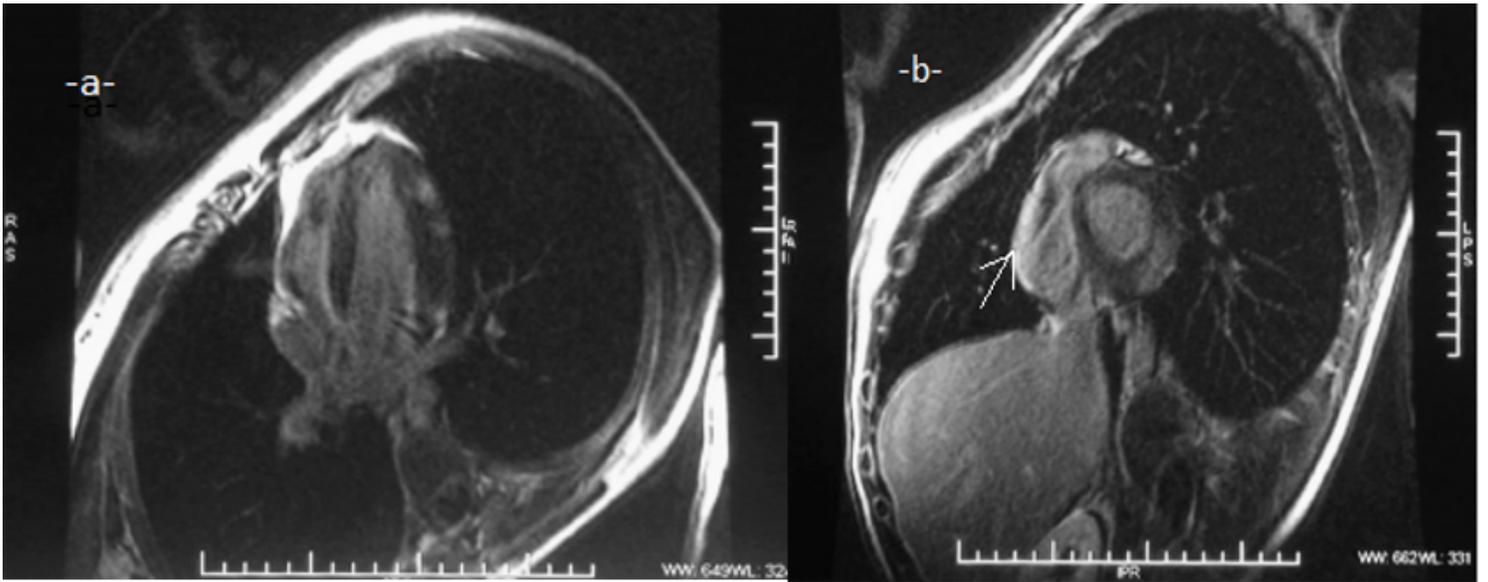


Figure 2

Cardio-vascular magnetic resonance (CMR) images in two short axis views in patient number 1 with suspected myocarditis. a) Early gadolinium enhancement antero-laterally in the sub-epicardial region b) signal intensity increase in T2-weighted images in the anterior aspect of the heart.

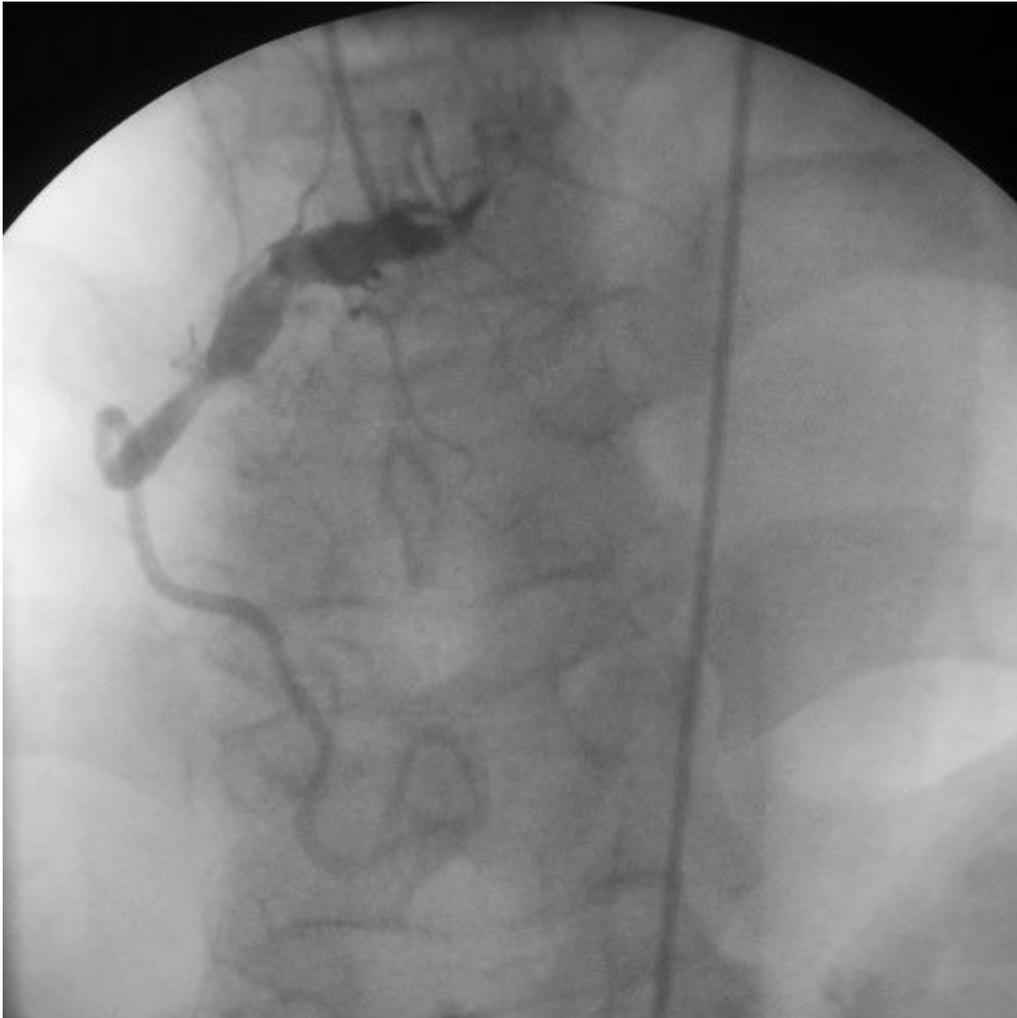


Figure 3

Left Anterior Oblique coronarographic incidence in patient 5 showing a totally occlusive thrombotic aneurysmal lesion of the second segment of the RCA.