Getting to the *heart* of the matter: diagnostic tools and therapeutic approach to cardiac involvement in Behçet syndrome A Tunisian case series

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SUMMARY

The aim was to investigate the frequency and spectrum of cardiac involvement (CI) in patients with Behçet syndrome (BS) in the Tunisian context, and to assess the clinical and imaging features, treatment, and outcomes.
We retrospectively retrieved the medical records of patients with CI among 220 BS patients admitted to the hospital internal medicine department between February 2006 and April 2019, who fulfilled the International Study Group diagnostic criteria for BS.
Ten patients (8 men, 2 women) were eligible for the study. Mean age was 37.3 years. Three patients had 2 isolated episodes of cardiac BS. The different types of CI were coronary artery disease (5/10), intracardiac thrombus (4/10), pericarditis (1/10), myocarditis (1/10), and myocardial fibrosis (1/10). Five patients had associated vascular involvement (50%). Medical treatment was based on corticosteroids and colchicine in all patients (100%), anticoagulants in 8 (80%), and cyclophosphamide followed by azathioprine in 9 (90%). The clinical course was favorable in 9 patients; 1 patient died.
CI remains an important feature of BS because of its association with increased risk of mortality and morbidity. Therefore, early screening and detection with imaging methods are paramount. Also, better cooperation between rheumatologists and cardiologists could improve outcomes.

Key words: *Behçet syndrome, cardiovascular system, coronary artery disease, myocarditis, immunosuppressive agents.*

■ BACKGROUND

Behçet's syndrome (BS) is an idiopathic, chronic, multisystemic vasculitis of unknown etiology, characterized by a remitting-relapsing course and a wide spectrum of clinical manifestations (1). It is more common and often more severe along the historic Silk Road (from Eastern Asia to the Mediterranean region). Mean age of onset is between 20 and 40 years (2). The prevalence in males and females varies among regions, but the incidence is usually higher in males (3, 4).
Vascular involvement is the hallmark of BS. It affects arteries and veins of different caliber, and is reported in more than 40% of patients with BS. Cardiac involvement (CI) is a rare and potentially fatal complication. The types of CI reported to date include pericarditis (1.6% of patients), intracardiac thrombi (2% of patients), coronary artery disease (0.5% of patients), active valvulitis (<2% of patients) and myocarditis (<0.5% of patients) (5-10).
Given the potential mortality and morbidity of cardiac manifestations and the lack of a well-codified treatment protocol (11), a better understanding is needed of their clinical characteristics, severity, and management. The aim of this study was to investigate the prevalence, clinical spectrum,

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imaging features, treatment, and outcomes in patients with BS who also had CI in the North African region.

■ PATIENTS AND METHODS

This study was approved by the institutional committee of Fattouma Bourguiba University Hospital in accordance with the ethical standards of the Declaration of Helsinki. We conducted a single-site, retrospective study based on a sample of 220 patients with BS admitted to the internal medicine department of Fattouma Bourguiba University Hospital between February 2006 and April 2016.

The inclusion criteria were (a) patients who fulfilled the International Study Group (ISG) criteria for BS (12), and (b) patients who were symptomatic at presentation (*i.e.* if at least 1 of the following symptoms was present: chest pain, palpitations, dyspnea, pericardial friction rub, heart murmur, or symptoms of right/left cardiac failure) and had CI classified according to the type of lesion: pericarditis, myocarditis, endomyocardial fibrosis, intracardiac thrombus, or myocardial infarction. Cardiac involvement was considered to be related to BS, if it was concomitant with BS flares. We excluded patients who did not fulfill the ISG criteria for BS, and those who had other known causes of cardiac disease. Cardiac involvement was mainly diagnosed based on clinical grounds, and on electrocardiographic and imaging techniques including echocardiography, chest computed tomography, cardiac magnetic resonance imaging, and percutaneous coronary angiography. Pathology investigations were also helpful in highlighting some specific manifestations.

Baseline demographic data and detailed clinical and laboratory data were collected from each patient's standard hospitalization documentation and medical records. Outcomes were evaluated for each patient and were classified as complete remission, partial remission, or death. Complete remission was considered as the absence of symptoms or cardiac lesions after therapy; partial remission was defined as persistent cardiac lesion with or without relapse despite treatment.

Table I - Demographic characteristics and criteria for Behçet syndrome.

Parameters	All patients, n=10
Gender (male/female)	8/2
Mean time since the diagnosis of cardiac involvement (years)	2.3 (range 1-9)
Clinical features:	
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%)
Arterial involvement (%)	3 (30%)
Venous involvement (%)	3 (30%)
Gastrointestinal involvement (%)	2 (20%)

■ RESULTS

Baseline characteristics of 10 patients with cardiac involvement

The main characteristics of the patients selected in our study are summarized in Table I. Patients were mostly male (80%), and mean age was 37.3 (range 20-49) years. Three of them had two episodes of cardiac BS. Cardiac involvement was the main manifestation of BS in three patients: one patient was diagnosed retrospectively after an intracardiac thrombus (ICT) was found, whereas coronary artery disease (CAD) was the initial presentation in the other two patients. In 7 patients, CI appeared during the course of the disease, up to 2.3 (range 1-9) years after the onset of BS.

Cardiac lesions

The characteristics of cardiac lesions, treatments and outcomes in patients with BS are summarized in Table II. The different types of CI were CAD (5/10) (one patient presented two episodes), ICT (4/10), myocarditis (1/10), pericarditis (1/10), and myocardial fibrosis (1/10). The main symptoms were chest pain (80%), tachycardia (60%), fever (60%), and dyspnea (50%). One patient with ICT associated with pulmonary embolism presented with symptoms of cough (10%) and hemoptysis (10%), while another had syncope (10%). Cardiac murmur was found in 3 patients (30%), and superior vena cava syndrome in 1 (10%). Two patients presented with heart failure symptoms (20%). Clinical examination also revealed an active

Table II - Characteristics of lesions, treatment and outcomes in patients with Behçet syndrome and cardiac involvement.

Case	Gender	Age at CI diagnosis (years)	Cardiac lesion	Vascular involvement	Treatment	Follow-up (years)	Outcome
1	Male	33	Myocarditis	None associated	Colchicine, CS, IS, Antiplatelet	2	Complete remission
2	Male	29	Cardiac thrombosis	Inferior vena cava thrombus, pulmonary embolism	IS, Colchicine, CS, AC	10	Partial remission
		39	Coronary stenosis		Colchicine, CS, AC, IS, PTCA	4	Partial remission
3	Male	20	Pericarditis	Pulmonary embolism and aneurysm, cerebral thrombosis, superior vena cava thrombus, occlusion of the right brachiocephalic artery	NSAIDs, Colchicine, CS	1	Complete remission
		21	Cardiac thrombosis		AC, Colchicine, CS, IS	13	Complete remission
4	Female	47	Cardiac thrombosis	None associated	AC, CS, IS, Colchicine	10	Complete remission
5	Male	37	Coronary aneurysm	None associated	CS, IS, Colchicine	2	Partial remission
		39	Coronary stenosis		CS, PTCA, AC, IS, Colchicine	13	Complete remission
6	Female	34	Cardiac thrombosis	Deep venous thrombosis (lower limb)	AC, CS, IS, Colchicine	3	Complete remission
7	Male	39	Endomyocardial fibrosis	Superior mesenteric artery aneurysm	ATB, CS, IS AC, Antiplatelet, Colchicine	1	Death
8	Male	49	Coronary stenosis	None associated	CS, IS, Colchicine, PTCA	2	Partial remission
9	Male	43	Coronary stenosis	None associated	CS, IS, Colchicine, PTCA	16	Complete remission
10	Male	42	Coronary stenosis and aneurysm	Occlusion of the right brachiocephalic artery	CS, IS, Colchicine, CABG	2	Complete remission

ATB, antibiotics; CS, corticosteroids; IS, immunosuppressants; AC, anticoagulants; NSAIDs, non-steroid anti-inflammatory drugs; PTCA, percutaneous transluminal coronary angioplasty; CABG, coronary artery bypass grafting.
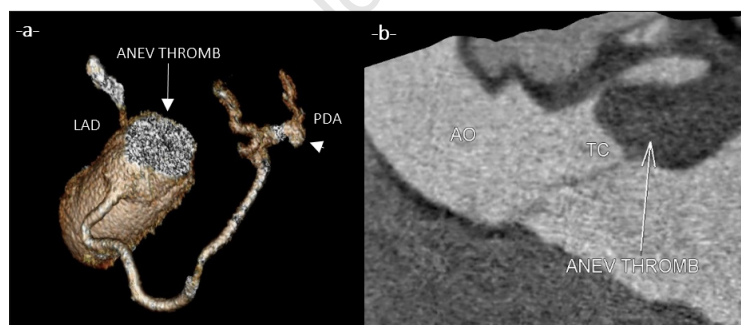

Figure 1 - Computed tomography (CT) coronary angiogram of patient number 10: (a) Three-dimensional surface-shaded display showing a giant thrombosed aneurysm in the left anterior descending artery (LAD) (arrow) associated with pre-occlusive stenosis and a posterior descending artery (PDA) aneurysm (arrowhead). (b) Oblique planar image of the aorta depicting stenosis in the left main coronary artery with thrombosis extending to the Valsalva ostium. ANEV THROMB, thrombosed aneurysm; LAD, left anterior descending artery; PDA, posterior descending artery; AO, aorta; TC, main left coronary artery.

phase of BS, with more than one of the following symptoms: uveitis, skin lesions such as erythema nodosum, genital ulcers, oral aphthosis, arthralgia, intestinal ulceration, progressive central nervous system lesions, and progressive vasculitis. Laboratory tests revealed increased inflammatory markers in 5 patients (50%). Coagulation profile (anti-phospholipid antibodies, factor V Leiden, prothrombin mutation, and homocysteine levels) was investigated in 5 patients (50%), and was positive in 2 of them (20%). Anti-cardiolipin antibodies were positive in the patient with endomyocardial fibrosis, and an elevated homocysteine level was noted in 1 patient with ICT.
Coronary angiography was highly informative in patients who had evidence of

CAD. Four of them had non-ST-elevation myocardial infarction, and 1 had lateral ST-elevation myocardial infarction. Smoking was the main cardiovascular risk factor in 1 patient; no other atherosclerotic risk factors were identified. Coronary artery lesions involved the right coronary artery in 2 patients, the circumflex artery in 1 patient, the left anterior descending artery in 2 patients, and the main left coronary artery in 1 patient. A large thrombosed

Figure 2 - 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 a thrombus in the right atrium, and two thrombi in the right ventricle (arrows). (b) Transesophageal echocardiography showing the right atrium thrombus. (c) Complete resolution of the thrombi after treatment (58).

aneurysm of the left anterior descending artery and a posterior descending artery aneurysm were identified in patient number 10 (Figure 1), and right coronary artery aneurysm was identified in patient number 5. Electrocardiography was performed in all patients, and was a key tool for CAD diagnosis. Among other incidental findings in all patients, there were left ventricular enlargement in two patients (20%), incomplete right bundle-branch block in one patient (10%), and premature ventricular complexes in another one (10%).

In 4 patients, ICT was identified, and was located mostly in the right chambers of the heart (3/4, 75%). The diagnosis was established by transthoracic echocardiography combined with transesophageal ultrasound in 3 patients. Computed tomography was used to confirm the diagnosis of ICT as well as to scrutinize the vascular system. In patient number 3 these techniques revealed a double ICT (right atrium + ventricle) (Figure 2) associated with partial obstruction of the superior vena cava, and also disclosed pulmonary artery thrombosis and aneurysms. Right atrial thrombosis extended to the vena cava in two patients (20%). Plasma homocysteine was elevated in patient number 2 (27 µmol/L).

Pericarditis was diagnosed in patient number 3 concurrently with genital and oral aphthae. Transthoracic echocardiography showed moderate pericardial effusion (10 mm anteriorly, 15 mm posteriorly).

Myocarditis was suspected in patient number 1, who presented with pleuritic chest pain and fever. Echocardiography showed left ventricle hypokinesis, and cardiac magnetic resonance imaging confirmed the diagnosis (Figure 3).

Endomyocardial fibrosis was retrospectively identified by histological examination of the mitral valve after its replacement in patient number 7, who was initially misdiagnosed for infective endocarditis following surgery for a superior mesenteric artery aneurysm. The same patient had positive antiphospholipid antibodies (anti-cardiolipin IgM 100 UI and IgG 7 UI) along with normal coagulation tests.
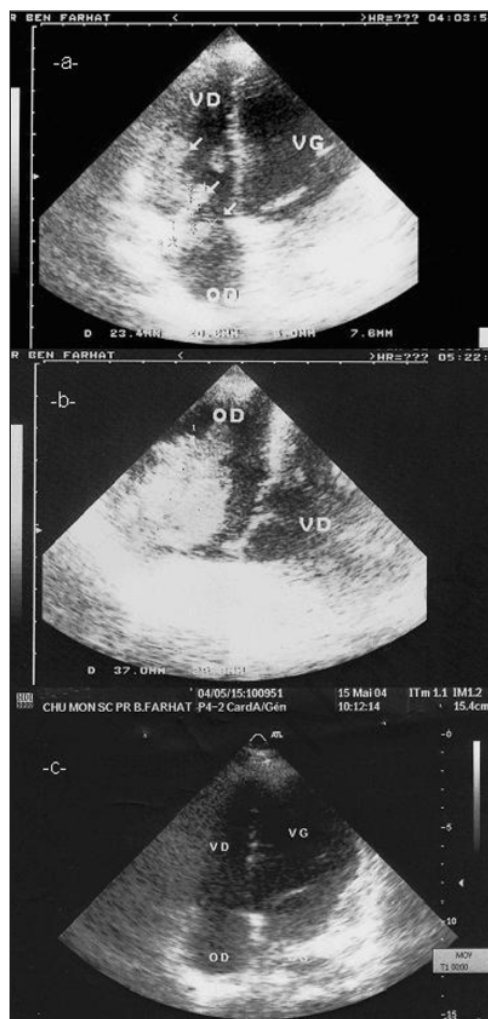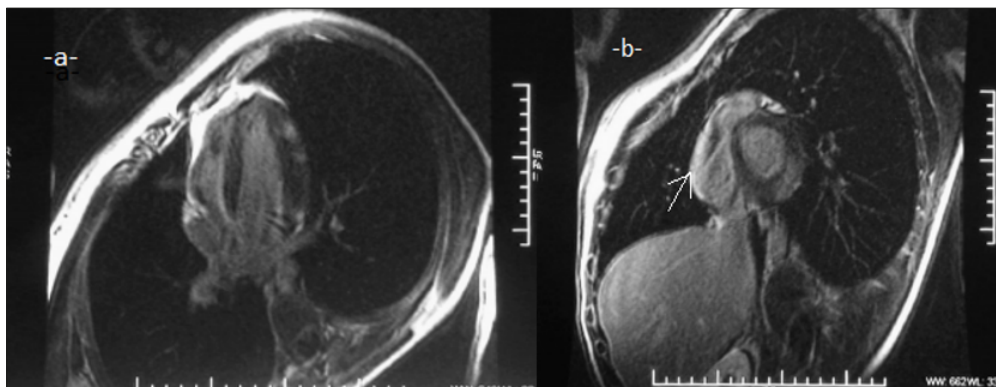
Figure 3 - Cardiovascular magnetic resonance images in two short axis views in patient number 1 with suspected myocarditis. (a) Early gadolinium enhancement anterolaterally in the subepicardial region. (b) Signal intensity increase in T2-weighted images in the anterior aspect of the heart (arrowhead).

Treatment and outcomes in Behçet syndrome patients with cardiac involvement

Medical treatment was based on colchicine (1 mg/day) associated with corticosteroids in all patients. The regimen consisted of 3 daily intravenous pulses of methylprednisolone 1000 mg/day followed by oral prednisone (1 mg/kg daily), which was gradually tapered over 6 months. Six-month pulses of cyclophosphamide followed by azathioprine were administered in 9 patients (90%). Three patients (30%) had a second 6-month course of cyclophosphamide due to the recurrence of their CI. Azathioprine was started in one patient (10%). All patients with BS and ICT received anticoagulants. Complete remission was obtained in 3 out of 4 patients, and the thrombus persisted in one patient. All patients with myocardial infarction benefited from coronary angiography: 3 out of 5 were successfully treated by percutaneous transluminal coronary angioplasty, and patient number 10 underwent a double coronary artery bypass grafting procedure. No complications were noted after the procedures. Patient number 5 relapsed after 2 years, with right coronary artery stenosis. Two out of 5 patients developed ischemic cardiomyopathy. Pericarditis was treated with nonsteroid anti-inflammatory drugs and corticoids. Antibiotics and surgical valve replacement were indicated in patient number 7, who experienced severe heart failure and died despite immunosuppressive therapy. The other 9 patients are currently being monitored with regular clinical and laboratory follow-up.

■ DISCUSSION

Behçet syndrome is a chronic inflammatory disease of unknown origin (1, 13). It is characterized by recurring flares of acute inflammation marked by oral aphthae and other systemic manifestations including mucocutaneous, ocular, neurologic, gastrointestinal, and cardiovascular symptoms (3, 4).
Although CI remains rare in most cross-sectional studies (5), this manifestation may persist long after disease activity is suppressed, and may have deleterious consequences in terms of damage accrual in the short term along with a substantial impact on morbidity in the long run (14). As reflected in the internationally developed tool to assess damage in BS, it has been increasingly recognized that CI is an important aspect of the course of the disease, which frequently exceeds other manifestations in mortality and morbidity rates (15). Therefore, its poor prognosis should be addressed and recognized by physicians who care for patients with BS.
The present study describes an array of cardiac manifestations, with a focus on clinical manifestations, treatments and outcomes.

It is among the first studies in the North African region to document a particular propensity for CAD, considered an infrequent manifestation of BS (10, 16). Vasculitis is the hallmark of the disease pathogenesis, and is thought to be the prime mover of cardiac lesions (17). In this connection, activated neutrophils cause excessive oxidative stress through increased levels of free radicals, such as superoxide anions, along with increased lysosomal enzymes, which eventually lead to destructive effects (18).

Cardiac involvement is a rare finding in BS, and has been reported in 0.13% to 16.5% of patients in previous studies. This frequency varies depending on the ethnic group and geographic locations (2, 3, 6, 9, 19-24) (Table III).

In the present study, mean age of patients with BS who had CI was 37.3 years, and male gender predominated (M:F = 4:1), suggesting that the prevalence of CI in males is higher than the overall relative prevalence of BS in men and women (M:F = 1.3:1) (25). Likewise, Wang et al. reported (3) that males accounted for 75% of all BS patients with ICT, and their mean age was 33.5 years. Hence, according to these observations, this severe manifestation of BS tends to occur more often in young adult men.

Cardiac features
Cardiac involvement may be the cardinal manifestation of BS, as was the case in 30% of our patients, a proportion in line with previous results (3, 6, 26). Therefore, a diagnosis of cardiac BS should be considered even in patients who do not show the classical criteria, particularly young male patients living in areas along the historic Silk Road.

Coronary artery involvement in BS is extremely uncommon. In fact, Ozeren *et al.* reported a prevalence of CAD less than 0.5% (27). Therefore, the importance of this study lies in highlighting the target population characteristics, the prognosis, and possible treatment cornerstones. As previously described, CI affects mainly young male patients without prominent atherosclerotic cardiovascular risk factors, who reside in countries traversed by the ancient Silk Road such as Turkey as well as countries in the Middle East, Mediterranean basin and parts of Asia (14, 28). Cardiac complications pose several diagnostic and therapeutic challenges. Indeed, the exact etiology leading to acute coronary events in patients with BS is not well known. Impaired microvascular function, arterial thrombi, and the presence of inflammation are believed to be the causes of coronary events in these patients (16). Nevertheless, there are several other etiologies that should be taken into account initially, such as primary atherosclerotic CAD, especially in adults with significant atherosclerotic risk factors, e.g. hypertension, dyslipidemia, diabetes, obesity, and smoking.

Coronary artery disease often manifests as myocardial infarction (6). The silent form hinders the diagnosis of this manifestation, which consequently is rarely reported. Indeed, 19.5% of patients with BS in a study by Turkolmez *et al.* had silent myocardial

Table III - Frequency of cardiac involvement in Behçet syndrome in the literature.

Author (country)	Year	Number of patients with BS	Cardiac involvement frequency
Lakhanpal (Japan) (21)	1985	170	16.5%
Assaad-Khalili (Egypt) (55)	1993	350	15%
Gurler (Turkey) (22)	1997	2147	0.13%
B'chir Hamzaoui (Tunisia) (23)	2006	519	2%
Geri (France) (6)	2012	807	6%
Zhang (China) (24)	2013	334	8,1%
Wang (China)(3)	2016	626	1.9%
This study	2020	220	4.54%

infarction compared to 2.9% of sex- and age matched of healthy control individuals (29). Lesions affecting the coronary arteries include stenosis, occlusion, in-stent stenosis, and aneurysm, the latter of which is the primary classic lesion in BS (26). Recurrent flares of BS are also associated with CAD involvement with repeated in-stent stenosis, aggressive progression, and elevated inflammation markers as seen in patient number 5, who had a recurrence of his CAD (30). Therefore, concurrent vascular involvement (*e.g.* patients 2 and 10) highlights the underlying vasculitis that goes hand in hand with coronary involvement (31).

We noted that 50% of patients cases had additional multifocal vascular involvement, i.e. pulmonary embolism, vena cava thrombosis, or right brachiocephalic artery occlusion. Among these patients, 2 had relapsing CI manifestations, which sometimes differed from the symptoms in their initial CI. Therefore, we emphasize that an initial cardiac event in a patient with BS is predictive of potential development of progressive multifocal vascular and cardiac complications (32).

Compared to venous thrombi, ICTs are relatively uncommon, and were reported in 1.9% of 626 BS patients in a study by Wang et al. (3). However, they were the second most frequent cardiac complication is our series (40% of cases), and this can be explained by geographic influence given that the Mediterranean basin is considered an endemic area (10). Usually, ICT occurs in males older than 40 years who do not receive adequate immunosuppressive therapy within 10 years of the diagnosis (3). However, it can also be the presenting sign of BS as observed in patient number 6 in the present study. The close association between vascular involvement and ICTs in our series is indicative of an ongoing inflammatory process: endothelium-dependent flow-mediated dilation is diminished, causing an increase in vascular inflammation. This leads to endothelial dysfunction which, along with thrombin and fibrin release, triggers thromboembolism (16, 33). Additionally, hyperhomocysteinemia

has been investigated in some studies as a predictor of BS activity; moreover, it may contribute to the pathogenesis of the disease, which could explain this finding in our series (20). As previously reported (2, 26), ICTs involved the right heart chambers more often than the left (3 right *vs*. 1 left atrial thrombus), perhaps because some thrombi have extended from the vena cava, and also because the lower pressure in the right heart predisposes toward blood flow stasis, one of the criteria in Virchow's triad. This is particularly important when considering the differential diagnosis, because heart tumors (myxomas) are frequently located in the left atrium (34). On the other hand, cardiac thrombi are also frequently misdiagnosed as infective endocarditis because of their indistinct features on echocardiography (*e.g.* vegetation-like lesions and echo-free spaces); hence, it is important to consider a differential diagnosis in case of an inadequate response to antibiotics along with a negative blood culture (35). Furthermore, right heart chamber thrombi are highly specific for BS (13, 36). Echocardiography along with computed tomography were highly informative in detecting ICTs, and the latter was also used as a screening tool for vascular involvement. In patient number 3, for example, computed tomography revealed pulmonary arterial aneurysms and thrombosis as well as a superior vena cava thrombus. This extremely rare entity is termed Hughes–Stovin syndrome (37).

In contrast to our study, pericardial involvement was reportedly the most common manifestation of BS in French cohorts, representing respectively 40% and 38.5% of CI in the studies by Wechsler et al. and Geri et al., respectively (6, 9). However, Pu et al. analyzed the echocardiographic findings in 63 Chinese patients with BS who had cardiac involvement, and found pericarditis in only one (10). We believe that differences among studies in the frequencies of pericarditis are inherent to the geographic characteristics of BS.

Because pericarditis is primarily due to viral agents (*e.g.* cytomegalovirus, Epstein-Barr virus, etc.), viral serology studies are

important in determining whether this CI should be attributed to BS (38). This complication can also be the cardinal presentation of BS, and although it may recur, it rarely leads to further complications such as constrictive pericarditis (6). Pericarditis can be symptomatic with stabbing chest pain, fever and dyspnea; in contrast, asymptomatic pericardial effusion can be detected as electrocardiographic abnormalities or with systematic echocardiography (19, 39, 40).

Endomyocardial involvement manifests mainly as valvular dysfunction or more rarely as endomyocardial fibrosis. In valvular involvement, the aortic and mitral valves are the most frequently affected (41). Clinically, valvular involvement can appear as an isolated acute or subacute manifestation, and is usually diagnosed by echocardiography. Endomyocardial fibrosis, on the other hand, is an exceptional, yet severe complication of BS. In fact, according to a 1985 study based on the Japanese autopsy registry, among 170 autopsies of patients with BS, only 2 disclosed this cardiac lesion (21). Endomyocardial fibrosis usually presents as symptoms of right heart failure, and is diagnosed during pathology examination of biopsy specimens (as at our tertiary care center, for example). It can also be misdiagnosed as infective endocarditis. Accordingly, if the presentation is incomplete and echocardiographic findings are present, the major Duke criteria may be met, resulting in delayed diagnosis, a worse prognosis, and a possibly fatal outcome, as in our series (10, 14). Failure to respond to antibiotics along with evidence from pathology studies of biopsy specimens are tools that can confirm the presence of fibrosis. This manifestation has been associated with anti-cardiolipin antibodies, which may have contributed to the pathogenesis of fibrosis; however, the relevance of this association is still unknown (42).

Isolated myocarditis is rarely reported in BS, and was found in only 1 case among 807 European patients with BS in a study by Geri et al. (6). Nevertheless, the frequency of myocardial involvement may be underestimated, given that it is reported more often in studies where patients underwent systematic screening with imaging techniques such as echocardiography or scintigraphy (10, 20). The diagnosis should be suspected, after ruling out other causes of myocarditis (viral, giant cell myocarditis, etc.), in patients with symptoms of heart failure, conduction abnormalities, or kinetic abnormalities on ultrasound (43-45). Cardiac magnetic resonance imaging has become an essential aid in diagnosing myocarditis owing to its ability to facilitate objective assessments of myocardial inflammation (46).

The aim of treatment for CI in BS is to decrease morbidity and mortality by repressing inflammation and thus preventing permanent organ damage. However, the European League Against Rheumatism (EULAR) provides limited information about CI in their BS management guidelines (2018 edition), and most of this document deals with its research agenda (11). Hence treatment remains mainly at the physician's discretion, and is still based on a low level of evidence (14, 19).

In the present study, remission of CI was associated with corticosteroids and immunosuppressive drugs, with cyclophosphamide and azathioprine being the most widely used. Nevertheless, this finding should be interpreted with caution because of the inherent differences between CIs. Treatment for CAD in the context of BS can be very challenging and often burdensome. For example, anticoagulants and thrombolytics may precipitate bleeding in aneurysms (47), and glucocorticoid pulses can curtail the heart healing process, rendering the organ more prone to rupture (14, 48). The cornerstone of CAD treatment remains the early implementation of anti-inflammatory agents, especially before mechanical manipulation of the coronary vessels (surgery or angioplasty), which could cause what is known as '*vascular pathergy*', which can be very risky (30). Similarly, caution is needed in the management of endomyocardial involvement, particularly in the preoperative course of surgical excision (49). The prognosis of CAD is usually poor, as it can lead to ischemic cardiomyopathy or

ventricular aneurysms and, in severe cases, to the rupture of coronary aneurysms and death (6). The combination of anticoagulants, glucocorticoids and immunosuppressants was effective in treating ICTs at our tertiary referral center. Other physicians also use remote thrombolytics for mobile clots (19). However, if the ICT is associated with a pulmonary artery aneurysm, it must be treated with intensive immunosuppressive therapy, and anticoagulants should be given cautiously because of the risk of bleeding. Transcatheter embolectomy may be beneficial in such cases (2-4, 19). Moderate pericarditis can be treated with non-steroid anti-inflammatory drugs, and less frequently with immunosuppressive agents if recurrent (4). For example, colchicine, indicated in all cases of BS, has been reported to be an efficient treatment for pericarditis regardless of its etiology, even when it recurs (50). The outcome in our series was favorable; however, relapses were frequently reported in other studies (6). Myocarditis is a rare complication of BS, and treatment is mainly focused on managing heart failure and arrhythmias, with glucocorticoids and immunosuppressants as adjuvants.

Anti-TNFα antibodies and interferon-alpha have proven efficacious in patients with BS who have severe ocular involvement (_i.e._ panuveitis) (51, 52). Furthermore, the EULAR recommendations for managing BS increasingly encourage the consideration of immunologic treatments for extraocular complications refractory to immunosuppressants (_e.g._ neurological and vascular involvement) (11). Indeed, according to a study by Desbois et al., anti-TNFα agents represent a safe and effective therapeutic approach for patients who have BS with major vessel involvement, leading not only to a steroid-sparing effect, but also prolonging the time to relapse (53). In light of these findings, we believe that biological agents can be beneficial for refractory CI; however, the evidence is still scarce and is mainly based on case reports (54). Therefore, future prospective studies and randomized controlled trials are required to verify the effectiveness of these treatments in the management of cardiac BS.

Overall, survival in BS patients with CI is unfavorable compared to patients without CI. Global 5-year mortality from BS is estimated at 5.4%, and reaches 15.4% to 20% in patients with CI (5, 55). The prognosis is better in patients who receive an earlier diagnosis, especially with the early use of anti-inflammatory drugs. We recommend that patients who are diagnosed with or suspected to have BS, particularly young males living in endemic areas, should be followed up routinely for CI. Imaging techniques such as echocardiography or angiography are potentially very helpful as screening methods for follow-up. We also propose a standardized approach based on cooperation between cardiologists and rheumatologists, in which synergistic decisions can be made that may well improve the patient's outcome.

We believe that CI is the result not only of an inflammatory process but also of a strong underlying genetic background in patients with BS. In recent years, it has been postulated that platelet-neutrophil complexes (PNC) may be closely connected with vascular and cardiac involvement in BS (thrombosis-inflammation-aneurysm). More prospective studies are needed to investigate this possible link, given that knowledge of the target genes may lead to new treatment approaches (56).

The limitations of our study include the small cohort due to the rarity of the disease and its retrospective nature. Prospective enrollment would have been ideal; however, this is very difficult to achieve with rare diseases. We also note that echocardiography, which may facilitate the diagnosis of asymptomatic BS in patients with CI, was used only in patients with symptomatic BS, but was not used systematically in the entire original sample of 220 patients. Moreover, all patients were enrolled from a single tertiary care center, so potential selection bias cannot be ruled out. Large prospective case-controlled studies are thus warranted to address these limitations.

Finally, despite being a rare manifestation of BS, CI remains a striking complication marked by high mortality and morbidity rates. Therefore, CI should be recog-

nized in the early course of the disease, and treated accordingly. Nevertheless, the most widely used criteria for BS (ISG) date from 1990 (12) and do not consider specific organ involvement such as CI. In our cohort, 3 patients had CI as the cardinal manifestation, and their cardiac symptoms delayed the diagnosis of BS, because they did not fulfil the ISG criteria. Therefore, efforts to diagnose BS should be tailored on a case-by-case basis even when the classic diagnostic criteria are not met. The International Criteria for Behçet's disease (ICBD) 2014 criteria (57) encompass a more specific organ involvement-oriented approach (e.g. vascular and neurologic involvement), and may be useful in improving the sensitivity of diagnostic criteria for BS (58).

■ CONCLUSIONS

Cardiac involvement, despite its rarity in BS, is among the most severe complication of this disease. It is more often present in young males, and may affect all three cardiac tunics and the coronary arteries. Echocardiography is the major radiologic imaging techniques that can provide efficient early screening of asymptomatic patients who live in areas along the Silk Route. The prognosis for cardiac complications is worse than for any other systemic manifestation of BS. Therefore, early diagnosis and treatment are paramount to improving survival rates. We believe closer cooperation between rheumatologists and cardiologists is a potentially important contributor to better clinical management of cardiac involvement in patients with BS.

Authors' contributions
ASH conceived this study; ASH and MJ analyzed and interpreted data, and drafted the manuscript; SD and SA contributed to data acquisition and collection; SO and KBH revised the manuscript. All authors read and approved the final manuscript.

Conflict of interests
The authors declare no potential conflict of interests.

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