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Review Article

Diagnosis of Behçet's Disease in Patients with Intracardiac Thrombi: A Real Big Challenge

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Abstract

Objective: To conduct a systematic review of published case reports and case series on the management of intracardiac thrombi (ICT) in patients with Behçet's disease (BD).

Methods: Medline, EMBASE, and Google Scholar databases were searched for case reports and case series published 2000 to 2014 reporting cases of BD complicated by ICT. Keywords included Behçet's disease, intracardiac thrombi, and cardiac involvement in BD. Reports published in English, French, Spanish, and Portuguese were included.

Results: A total of 154 of BD complicated by ICT were published from 2000 to end of 2014. Sixty-seven cases were described in case series while 77 case reports were available for analysis. The most commonly reported clues and keywords that were mentioned in these reports to describe the clinical picture of patients with BD and ICT were dyspnea, fever, hemoptysis, right sided cardiac thrombi, associated pulmonary artery aneurysms, high incidence of pulmonary thromboembolic events, systemic venous occlusion, orogenital ulcers, elevated inflammatory markers, recurrence following surgical resection, and death due to fatal hemoptysis. Thirty-five percent of patients did not fulfill the international study group criteria for diagnosis of BD. Diagnosis was made based on the presence of orogenital ulcers with or without manifestations of other systems affection. About one third of the patients had undergone surgical resection of the ICT. The majority of these cases were not diagnosed as BD prior to the surgical intervention. The diagnosis of BD was made retrospectively based on the histopathological findings or following recurrence, and post-operative appearance of orogenital ulcerations.

Conclusion: Concerning the management of ICT in BD, it seems that establishing the diagnosis is the most challenging part of the story. The early dermatological/rheumatological consultation for all patients presenting with ICT would help in early establishment of the diagnosis and might avoid extensive -occasionally unnecessary- investigations and surgical procedures.

INTRODUCTION

The diagnosis of Behçet's disease (BD) is extensively based on clinical features due to the lack of specific laboratory and imaging findings [1]. Several diagnostic criteria have been proposed for establishing the diagnosis of BD. The sensitivity and specificity of these suggested criteria are basically different. In a previous study aiming at comparing the sensitivity and specificity of various proposed diagnostic criteria of BD, Cheng & Zhang criteria showed the highest sensitivity (100%) but also the least specificity (74.2%) for diagnosis compared to the other criteria. Hamza criteria were more sensitive and more specific for making a diagnosis (98.2% and 100%) compared to both the international study group (ISG) and Japanese criteria. Dilşen criteria were also found to be more sensitive and more specific compared to the Japanese criteria [2]. Still, ISG are the most frequently used criteria for diagnosing BD. According to the ISG criteria, the diagnosis of BD should be made based on the presence of recurrent oral ulceration (at least 3 times in one 12-month period) plus any of two other findings including recurrent genital ulceration, specific eye lesions, specific skin lesions, and a positive pathergy test. Recently and in order to increase the sensitivity of ISG criteria, a new set of diagnostic criteria has been established with the addition of both the vascular and neurological manifestations [3].

Intracardiac thrombi (ICT) in an otherwise structurally normal heart were reported in patients with BD. Occasionally, these thrombi may precede the other manifestations of the disease. Moreover, the appearance of oral ulcers (considered as an obligatory criterion in the ISG for BD diagnosis) may be detected only following the surgical resection of the thrombi [4-6]. Additionally, a group of other clinical manifestations as pulmonary artery aneurysms, pulmonary thromboembolic events, and systemic venous occlusions were commonly detected in patients with BD and ICT [5,7-9]. This systematic review analysed the data from all case reports and case series published 2000 to 2014 to describe the management of patients with BD and ICT.

MATERIALS AND METHODS

Medline, EMBASE, and Google scholar databases were searched for case reports and case series published 2000 to end of 2014 reporting cases with BD complicated by ICT. Keywords included Behçet's disease, Adamantiades-Behçet's disease, intracardiac thrombi, intracardiac masses, right ventricular thrombi, right atrial thrombi, cardiac thrombosis, cardiac pseudotumor, and cardiac involvement in BD. Case reports published in English, French, Spanish, and Portuguese were included. Bibliographies of all available articles were reviewed for all possible relevant ones.

RESULTS

A total of 154 cases with BD complicated by ICT were published from 2000 to end 2014 [4,5,7-86]. Seventy-seven case reports with full texts [5,7,9-70] were available for further analysis (Table 1) Sixty-seven cases were described in case series. The majority of reported patients in the available case series had thrombi in the right side of the heart and associated pulmonary thromboembolic events. Patients from Sultanate Oman had associated pulmonary artery aneurysms and were treated adequately without the concomitant use of anticoagulation [76]. In one case series from China, 30% of patients did not fulfill the ISG criteria at the onset of the cardiac complication [75]. Forty-four percent of patients in the case series from France were originated mostly from North Africa. 60% of cases had evidence of pulmonary thromboembolic complications and all patients received anticoagulation. Two patients underwent surgical resection of the cardiac masses while the ICT resolved in the remaining 8 patients who received corticosteroids, azathioprine and anticoagulation [73].

Seventy-six percent of case reports were from the Mediterranean basin (n=59 patients), 27 patients (44%) were from Turkey, 17 from North Africa (29%), and 9 from Southern Europe (15%). Mean age of patients was 28.7±10 years. The youngest case (9 years) was from the Mediterranean basin while the oldest was from Japan (68 years). Fifteen patients were females (19%). The overall male to female ratio is 4:1 but higher in patients from Mediterranean basin (5.5:1). Forty percent of females were diagnosed as BD prior to the development of ICT, on the other hand, only 11% of males were previously known cases of BD although the mean age of both males and females was comparable (29±11 versus 28±8, p= 0.6). Only 13 patients were diagnosed as BD before the appearance of the ICT. The treatment was mentioned in only 5 cases, 2 were on both corticosteroids and colchicine, two were non-compliant to colchicine therapy, and the last one was on irregular corticosteroid therapy.

The most commonly reported symptoms were fever, shortness of breath, hemoptysis, chest pain, weight loss, and cough (52%, 43%, 38%, 29%, 23%, and 22% respectively). Other less frequently mentioned symptoms included palpitations, fatigue, edema, and abdominal complaints. Mean duration of symptoms was 81±95 days (range: 1 to 500). Nineteen patients (25%) had previous thrombotic events affecting the veins of the lower limbs (n=10), the cerebral veins (n=4), the heart (n=3), and the inferior vena cava (n=2).

Thirty-four patients (44%) had skin lesions, the majority were in the form of papulopustular eruption and pseudofolliculitis. Examination of the eye was mentioned in only 27 patients, 52% of them (n=14) showed no abnormalities. Pathergy test was available in only 37 reports being positive in 61% (n=21). A summary of the laboratory investigations is shown in Table 2.

The interpretation of chest X-ray was available in 46 cases, being abnormal in 33 patients (71%). The most commonly detected abnormalities were pulmonary opacities/consolidation (n=15), hilar enlargement (n=12), and pleural effusion (n=3). Computed tomography (CT) data were available in 70 patients. Pulmonary thromboembolism, pulmonary aneurysms, intracardiac thrombi, and systemic venous obstruction were the most commonly reported CT findings. Abnormal CT brain findings were detected in 3 patients. Systemic venous thrombosis was documented in 35 patients while only 7 patients had concomitant arterial lesions. Pulmonary thromboembolism was diagnosed using chest CT, lung perfusion scintigraphy, magnetic resonance imaging, and pulmonary angiography in two-thirds of patients.

Thirteen patients were previously diagnosed as BD. The criteria used for diagnosis of BD in the remaining 64 patients were as follows: thirteen patients (20%) had evident oral -with or without genital ulcerations- and 2 other major criteria (skin, eye lesions, or positive pathergy test). Twenty-four patients (37%) had orogenital ulcers and skin lesions, 3 (5%) had orogenital ulcers and a positive pathergy test, and only one patient was diagnosed based on the presence of ulcers and eye manifestations. The remaining 23 patients (35%) did not fulfill the ISG criteria for diagnosis of BD. Diagnosis was made based on the presence of orogenital ulcers with manifestations of other systems affection as the cardiovascular and neurological systems. The suspicion of BD was made postoperatively based on the histopathological findings from surgically resected ICT (organized thrombus with or without associated inflammatory infiltration, and occasionally evidence of endomyocardial fibrosis), the recurrence of ICT, or the appearance of oral or scrotal ulcers following surgery.

Seven patients had abnormal left ventricular findings by echocardiography (thrombi in 5 patients and impaired overall systolic function in 2). 60% of left ventricular thrombi (n=3) were complicated by systemic embolization (cerebral vessels=2, popliteal artery=1). Pulmonary thromboembolism was detected in only one patient with isolated left ventricular thrombus. Isolated right ventricular thrombi were detected in 41 cases. About 75% of them had concomitant pulmonary embolism. Twenty-one patients had right atrial thrombi (60% had pulmonary thromboembolism) while 9 patients had thrombi in both right atrial and ventricular chambers (88% of them had pulmonary thromboembolism). The intracardiac thrombi were mobile in 22 cases, 81% of these mobile thrombi were associated with pulmonary thromboembolism.

The most commonly prescribed drugs in addition to corticosteroids were anticoagulants (n=64), cyclophosphamide (n=40), colchicine (n=33), and azathioprine. Three patients died while on medical treatment. The cause of death (2 of them were on anticoagulants) was massive hemoptysis. 35% of patients

had undergone surgical resection of the ICT. The majority of these cases were not diagnosed as BD prior to the surgical intervention and diagnosis was made retrospectively based on the histopathological findings or following recurrence of the ICT, or the post-operative appearance of orogenital ulcerations. Following surgery, two patients died. One from massive hemoptysis developed 6 months later and the other from acute hepatic failure.

Table 1: Patient characteristics, symptoms, site, and management of intracardiac thrombi in patients with Behçet's disease

No	Study	Age	Sex	Symptoms	Site	Treatment	Outcome	Diagnostic clues
1	Vaya et al. [10]	16	M	Fever, dyspnea, hemoptysis	RV, RA	Surgery, LMWH, prednisolone, azathioprine	Recurrence after surgical removal	Orogenital ulcers, cardiovascular involvement
2	Basaran et al. [11]	28	M	Dyspnea, fatigue, leg edema	RV, RA	Surgery, steroids, cyclosporine, AC	Resolution of symptoms and thrombus following surgery	Orogenital ulcers, skin lesions, positive pathergy test
3	Baykan et al. [12]	33	M	Dyspnea, cough, hemoptysis	RV, RA	Heparin, steroids, colchicine, AC, cyclophosphamide	Reduced mass size	Orogenital ulcers, positive pathergy test
4	Özalti et al. [13]	27	M	Fever, chest pain, hemoptysis	RV	Surgery, heparin, steroids, colchicine, AC, antibiotics	Recurrence after surgical removal	Orogenital ulcers, skin lesions
5	Dincer et al. [14]	39	M	Fatigue, fever, weight loss	RA	Surgery, steroids, colchicine, AC, cyclosporine	Recurrence after surgical removal	Orogenital ulcers, skin lesions
6	Cemri et al. [15]	27	M	Dyspnea, hemoptysis, chest pain	RA	Steroids, AC, cyclophosphamide	Disappeared on medical treatment	Orogenital ulcers, skin lesions, positive pathergy test
7	Houman et al. [16]	29	M	Fever, chest pain, dyspnea, hemoptysis	RV	Surgery, steroids, colchicine, AC, cyclophosphamide	Recurrence after surgical removal	Orogenital ulcers, skin lesions
8	Ilvan et al. [17]	22	M	Dyspnea, hemoptysis, chest pain, cough	RV, RA	Steroids	Recurrence	Orogenital ulcers, pulmonary aneurysms
9	Goktekin et al. [18]	23	M	Hemoptysis, edema, confusion	RV, RA	Surgery, Steroids, cyclophosphamide, amphotericin B	Death due to hepatic failure	Orogenital ulcers, skin lesions
10	Altunkeser et al. [19]	29	F	Cough, dyspnea, palpitations	RA	Surgery, AC, aspirin	Recurrence after surgical removal	Known case of BD
11	Hassikou et al. [20]	38	M	Chest pain, hemoptysis	NA	Cyclophosphamide, steroids, heparin, antibiotics	Death due to massive hemoptysis	Known case of BD
12	Gönlügür et al. [21]	35	F	Fever, chest pain, cough, dyspnea	RV, RA	Surgery, AC	Death due to massive hemoptysis	Known case of BD
13	Gönlügür et al. [21]	27	M	Cough, dyspnea	RV	Steroids, azathioprine	Both ICT and PAA disappeared.	Orogenital ulcers, PAA, arthralgia, DVT
14	Kaya et al. [22]	25	M	Fever, cough, hemoptysis	RV	Steroids, cyclophosphamide	Good response to medical treatment	Orogenital ulcers, skin lesions, positive pathergy test
15	Ben Ghorbel et al. [23]	33	M	Hemoptysis, chest pain, fever, dyspnea	RV	Surgery, steroids, colchicine, AC, cyclophosphamide	Recurrence after surgery	Orogenital ulcers, skin lesions
16	Ben Ghorbel et al. [23]	29	M	Dyspnea, heart failure	RA	Steroids, AC, colchicine	Persistence of symptoms. Patient refused surgical intervention	Orogenital ulcers, skin lesions, positive pathergy test
17	Ben Ghorbel et al. [23]	25	M	Hemoptysis	RA	Surgery, Steroids, AC, colchicine, cyclophosphamide, amiodarone, antibiotics	Recurrence after surgery	Orogenital ulcers, skin lesions, positive pathergy test
18	Hammami et al. [24]	20	M	Dyspnea, cough, hemoptysis	RV, RA	LMWH, steroids, colchicine, AC, cyclophosphamide	The mass disappeared	Orogenital ulcers, skin lesions, polyarthralgias
19	Hammami et al. [24]	29	M	Fever, loss of weight, chest pain	RA	Heparin, steroids, colchicine, AC, cyclophosphamide	The mass disappeared	Orogenital ulcers, skin lesions, positive pathergy test
20	Kaneko et al. [25]	46	M	Fever, leg swelling, right oculomotor nerve palsy	RA	Steroids, AC, cyclophosphamide	The mass disappeared	Orogenital ulcers, skin lesions
21	Darie et al.[26]	31	F	Fever, loss of weight	RV	Surgery, steroids, colchicine, AC, folic acid	Disappearance of the cardiac thrombus	Oral ulcers, skin lesions, eye findings

22	Atalay et al. [27]	36	M	Fever, hemoptysis, oral ulcer	RV	Steroids, cyclophosphamide	Death due to massive hemoptysis	Orogenital ulcers, skin lesions
23	Ernam et al. [28]	20	M	Dyspnea, hemoptysis, fever, partial loss of vision	RV	Steroids, AC, cyclophosphamide	The patient improved	Orogenital ulcers, eye lesion
24	Okumus et al. [29]	23	F	Dyspnea, hemoptysis	RA	Steroids, LMWH, AC, cyclophosphamide	Disappearance of the cardiac thrombus	Orogenital ulcers, positive HLA-B51
25	Dogan et al. [30]	33	M	Cough, fever, chest pain, hemoptysis, weight loss	RV	Steroids, AC, cyclophosphamide	Disappearance of the cardiac thrombus	Known case of BD
26	Kasifoglu et al. [31]	24	M	Fever, chest pain	RA	Steroids, AC, heparin cyclophosphamide	Disappearance of the cardiac thrombus	Orogenital ulcers, vascular thrombosis
27	Miranda et al. [32]	14	M	Fever, chest pain, hemoptysis, weight loss, dyspnea	RV	Surgery, steroids, AC, cyclophosphamide	The patient improved after surgery	Oral ulcers, skin lesions
28	Yakut et al. [33]	24	F	Cough, dyspnea	RV, RA	Steroids, AC, cyclophosphamide, colchicine	Regression of the ICT	Orogenital ulcers, vascular thrombosis
29	Vahedian et al. [34]	17	M	Fever, weight loss, fatigue, malaise	RV	Steroids, colchicine, AC, cyclosporine	Disappearance of the cardiac thrombus	Orogenital ulcers, skin lesions
30	Kayija et al. [35]	26	F	Fever, digital edema	RA	Surgery, steroids, colchicine, AC	Resolution of the mass	Orogenital ulcers, arthritis, positive HLA-B51
31	Endo et al. [36]	13	F	Intermittent leg pain, popliteal artery occlusion	LV, RV, RA	Surgery, urokinase, LMWH, Infliximab, cyclophosphamide	Recurrence after surgery, improved with medical treatment	Orogenital ulcers, arterial thrombosis, PAA
32	Leibowitz et al. [37]	34	F	Hemoptysis, dyspnea	RV	Steroids, azathioprine, cyclosporine	Complete resolution of the mass	Known case of BD
33	Leibowitz et al. [37]	20	M	Scrotal ulcers, PAA	RV	Steroids, AC, cyclophosphamide	Complete resolution of the mass	Genital ulcers, PAA
34	Leibowitz et al. [37]	45	M	Facial and neck swelling	RA	Steroids, AC	Complete resolution of the mass	SVC syndrome, ICT
35	Chang et al. [38]	54	M	Dyspnea, cough, fever	RV	Steroids, AC, cyclophosphamide, azathioprine	Initially, ICT disappeared on medical treatment but later, death due to massive hemoptysis	Known case of BD
36	Chiari et al.[39]	20	M	Dyspnea, fever, hemoptysis	RV	Steroids, AC, azathioprine, heparin, antibiotics	Disappearance of the cardiac thrombus	Orogenital ulcers
37	Houari et al. [40]	18	M	Dyspnea, cough, hemoptysis, fever, chest pain	RV	Steroids, AC, cyclophosphamide	Regression of the ICT	Orogenital ulcers, positive pathergy test
38	Takahama et al. [41]	68	M	Fever	RV	Steroids, colchicine	Disappearance of the cardiac thrombus	Orogenital ulcers, epididymitis, positive HLA-B51
39	Vivante et al. [42]	14	M	Fever, weight loss, skin rash, hemoptysis	RV	Steroids, LMWH, colchicine, cyclophosphamide	Disappearance of the cardiac thrombus	Oral ulcers, skin lesions, PAA
40	El Louali et al.[43]	30	M	Dyspnea	RA	Heparin, steroids, colchicine, AC, cyclophosphamide	Disappearance of the cardiac thrombus	Known case of BD
41	El Louali et al.[43]	52	M	Dyspnea	RV	Steroids, AC, cyclophosphamide	Disappearance of the cardiac thrombus	Oral ulcers, vascular lesions, positive pathergy test and HLA-B51 tests
42	El Louali et al.[43]	23	M	Hemoptysis	RV	Steroids, colchicine, AC, cyclophosphamide	Disappearance of the cardiac thrombus	Orogenital ulcers, positive HLA-B51
43	Jahdali et al. [44]	23	F	Hemoptysis, headache	RV	Steroids, colchicine, cyclophosphamide, AC, heparin, azathioprine	Favorable response to treatment	Oral ulcerations, papilledema
44	Moreno et al. [45]	24	M	Hemoptysis, chest pain, fever	RV	Surgery, steroids, colchicine, AC, azathioprine, antibiotics	Recurrence of the ICT	Orogenital ulcers, skin lesions
45	Piga et al. [46]	22	F	Right leg pain and swelling	RV	Surgery, steroids, AC, LMWH, streptokinase	Disappearance of the cardiac thrombus	Orogenital ulcers, skin lesions
46	Sacre et al. [47]	49	M	Dyspnea	LV	Steroids, colchicine, azathioprine, AC, cyclophosphamide	Regression of the ICT	Orogenital ulcers, skin and eye lesions

47	Adams et al.[48]	16	M	Fever, malaise, fatigue, chest pain	RV	Surgery, steroids, AC, heparin, colchicine, methotrexate	Disappearance of the cardiac thrombus	Oral ulcers, folliculitis, arthritis
48	Hiwarkar et al. [49]	22	F	Fever, night sweats, swelling and pain in the right leg	RV	Surgery, LMWH, steroids, AC, lepirudin streptokinase	Persistence of the mass following surgery	Oral ulcers, skin lesions, extensive thrombosis
49	Solmaz et al.[50]	35	M	Facial swelling	RA	Immunosuppressive therapy, AC	NA	Orogenital ulcers, skin lesions, vein thrombosis
50	Kim et al. [51]	31	M	Abdominal pain on walking, arthralgia	RA	Heparin, Urokinase, steroids, AC	Disappearance of the cardiac thrombus	Orogenital ulcers, skin lesions, arthralgia
51	Gopathi et al.[52]	27	M	Dyspnea, cough, hemoptysis, weight loss, chest pain	RV	Steroids	NA	Oral ulcers, skin lesions, vascular involvement
52	Khammar et al. [53]	35	F	Lower limb venous occlusion	RV RA	Steroids, AC, colchicine	Favorable response to treatment	Oral ulcers, positive pathergy test, skin lesions
53	Khammar et al. [53]	46	M	Loss of weight, anemia, loss of appetite	RA	Steroids, colchicine, AC, azathioprine	Favorable response to treatment	Oral ulcers, conjunctival lesion, skin lesions
54	Khammar et al. [53]	40	M	Dyspnea, abdominal pain	LV	Steroids, AC, cyclophosphamide	Disappearance of the cardiac thrombus	Oral ulcers, venous occlusion
55	Thamothera et al. [54]	21	M	Blind eye, abdominal pain	RA	LMWH, AC, steroids, azathioprine	Disappearance of the cardiac thrombus	Orogenital ulcers, uveitis, positive pathergy test
56	Elqatni et al.[55]	30	M	Cough, hemoptysis, night sweats	RA	Steroids, AC, cyclophosphamide	Disappearance of the cardiac thrombus	Oral ulcers, skin lesions
57	Yeung et al.[56]	39	M	Night sweats, rigors, weight loss	RV	Steroids, azathioprine	Disappearance of the cardiac thrombus	Oral ulcers, skin lesions
58	Hammami et al. [57]	20	M	Fever	RV	Heparin, steroids, colchicine, AC, cyclophosphamide, interferone	Disappearance of the cardiac thrombus	Orogenital ulcers, skin lesions, positive HLA-B51
59	Canpolat et al. [9]	32	M	Cough, hemoptysis, sweating, loss of weight	RV	Heparin, steroids, colchicine, cyclophosphamide, AC	Disappearance of the cardiac thrombus	Orogenital ulcers, skin lesions
60	Malik et al. [58]	18	M	Fever, chest pain	RV	Surgery, steroids, azathioprine, AC	Favorable response	Scrotal ulcer, positive pathergy test, ICT
61	Yao et al. [59]	35	F	Fever, dyspnea	RV	Surgery, treatment of BD as prescribed by rheumatologists	Favorable response	Known case of BD
62	Duzgun et al. [60]	22	M	Fever, slurred speech, hypoesthesia on the left arm	LV	LMWH, steroids, colchicine, antibiotics, aspirin, cyclophosphamide	Disappearance of the cardiac thrombus	Orogenital ulcers, cerebral, pulmonary lesions, ICT
63	Duzgun et al. [60]	24	M	Fever, dyspnea	RV	Steroids, colchicine, cyclophosphamide	Disappearance of the cardiac thrombus	Known case of BD
64	Duzgun et al. [60]	25	M	Fever, abdominal pain	RA	LMWH, steroids, colchicine, antibiotics, cyclophosphamide	The mass reduced in size	Orogenital ulcers, skin lesions
65	Aşker et al. [61]	20	F	Cough, fever, palpitations, chest pain	RV	LMWH, steroids, cyclophosphamide	Partial resolution of the ICT	Known case of BD
66	Ghori et al.[62]	19	M	Fever, weight loss	RV	Surgery, heparin, AC, steroids, azathioprine	Disappearance of the cardiac thrombus	Orogenital ulcers, indurations at venipuncture sites
67	El Euch et al. [63]	33	M	Fever, chest pain, weight loss	LV	Surgery, steroids, colchicine, AC, antibiotics	Clinical improvement	Orogenital ulcers, neurological lesions, ICT
68	Neves et al. [64]	38	M	Chest pain, fever, cough, dyspnea, hemoptysis	RV	AC, steroids	Clinical improvement	Oral ulcers, skin lesions, positive pathergy test
69	Bouzelmat et al. [7]	26	M	Hemoptysis, dyspnea, loss of weight	RA	Steroids, cyclophosphamide, AC	Disappearance of the cardiac thrombus	Orogenital ulcers, skin lesions
70	Aksu et al. [65]	29	M	Dyspnea, palpitations, chest pain	RA	Heparin, steroids, colchicine, cyclophosphamide	Disappearance of the cardiac thrombus	Known case of BD

71	Dimitrios et al.[66]	32	M	Dizziness, headache, dyspnea, fever	RA	Surgery, LMWH, AC, aspirin, azathioprine, steroids, colchicine, folic acid	Disappearance of the cardiac thrombus	Orogenital ulcers, positive HLA-B51, positive pathergy test, eye lesions
72	Xing et al. [67]	43	F	Fever, cough, dyspnea, chest discomfort	RV	AC, antibiotics	The mass reduced in size	Known case of BD
73	Leibowitz et al. [5]	35	M	Fever, night sweats, headache	RV	Surgery, steroids, antibiotics, AC, azathioprine	Recurrence after surgical resection	Oral ulcers
74	Leibowitz et al. [5]	9	M	Fever, oral ulcers	RV	Surgery, steroids	Disappearance of the cardiac thrombus	Oral ulcers, recurrent thrombophlebitis
75	Aksu et al. [68]	33	M	Dyspnea, fatigue, weight loss	RV	Surgery, steroids, AC, colchicine	Recurrence after surgery	Recurrent ICT, oral ulcers, possible BD
76	Madureira et al. [69]	14	M	Fever, chest pain, oral ulcer	RV	Surgery, steroids, antibiotics, cyclophosphamide	Favorable response	Orogenital ulcers, skin lesions, positive HLA-B51
77	Ozcan et al. [70]	26	M	Cough, dyspnea, hemoptysis, weight loss	RV	Steroids, cyclophosphamide, azathioprine, colchicine	Favorable response	Known case of BD

Abbreviations: AC: anticoagulation; BD: Behçet's disease; ICT: intracardiac thrombus; F: female; LMWH: low molecular weight heparin; M: male; PAA: pulmonary artery aneurysm; RA: right atrium; RV: right ventricle; LV: left ventricle

Table 2: Laboratory findings in patients with BD

Laboratory findings	Value
Hemoglobin, gm/dl	10±1.7
White blood count	11.7±5
Erythrocyte sedimentation rate	78±36
C- reactive protein	76±81
Abnormal coagulation profile	5/41 (12%)
Positive HLA-B51	21/27 (88%)
Abnormal anti-nuclear/anti DNA tests	6/49 (12%)
Data is expressed as mean ± standard deviation, numbers, and percentages	

DISCUSSION

This systematic review showed that patients with BD and ICT had a worse prognosis. Five out of the 77 cases died with severe hemoptysis being the cause of death in 4 patients. This indicated that concomitant pulmonary aneurysms, rather than the ICT, are responsible for such high mortality [6]. The majority of patients with BD presented initially with ICT in this review had associated abnormalities in the form of pulmonary lesions (aneurysms, thromboembolism), venous obstruction (veins of the lower limbs, cerebral veins, superior and inferior vena cava), and elevated inflammatory markers. Occasionally, a positive HLA-B51 was detected and was used in the presence of orogenital ulcerations as a criterion for diagnosis of BD [35]. According to a previous systematic review, the frequency of pulmonary involvement in patients with BD and ICT is much higher than in those without ICT [6]. A possible concomitant endothelial/subendothelial injury involving both the heart and pulmonary arterial bed was suggested [21].

The most important challenge that faced physicians in many of the present reports was the diagnosis rather than the treatment of the disease. The diagnosis of BD based on some of these reports seems to be very difficult and required many – sometimes even unnecessary- investigations. We believe that 2 important causes might be the source of such difficulties. The first is the fact that the majority of patients with ICT and not previously known to have BD complained initially of shortness of breath, cough, hemoptysis, and fever so they were commonly referred to either a cardiologist, or a cardiothoracic surgeon rather than a specialist (rheumatologist/dermatologist) for further evaluation. Cardiologists/cardiothoracic surgeons may not consider the diagnosis of BD in these patients because the presence of ICT and associated pulmonary lesions could explain the patient's symptoms. Additionally, asking routinely about orogenital ulcers, and examination of the eye and skin to elicit the criteria of the disease (which was not considered in the differential diagnosis) do not belong to the daily patients' assessment in the cardiac/cardiothoracic surgical wards. The early referral of all patients with ICT to a rheumatologist/dermatologist, even in the absence of the manifestations of BD, could help and support the diagnosis of BD as early as possible [87].

The second source of difficulty in making the diagnosis of BD in patients with ICT is that the proposed ISG criteria for diagnosis of BD were not met in all the reported cases [5,41,43,48,60,63,75]. Orogenital ulcers occurred in some patients during their hospital stay or following the post-operative resection of the mass [4,5,10,13,46,58]. Moreover, some patients were not diagnosed as BD based on the proposed widely known and used ISG criteria for BD diagnosis [48,63]. Some were diagnosed based on the presence of orogenital ulcers and cardiovascular involvement, [13,29,60] the presence of orogenital ulcers and positive HLA-B51 tests, [41,43] or the orogenital ulcers, neurological, and cardiovascular involvement [20,63]. Furthermore, two reports have considered oral ulceration of less than 1-year duration as a criterion for diagnosis of BD [40,63].

In order to improve the clinical sensitivity of the ISG criteria, a new set of diagnostic criteria was proposed [3]. Recently, both vascular and neurological complications were added to the original ISG criteria for diagnosis of BD based on studying 2556 patients collected from 27 countries [88]. The role of ICT was not unfortunately mentioned. Whether to consider ICT as a vascular

manifestation is not clear. Furthermore, we do not know exactly how to calculate the score in patients with more than one vascular lesions; for example, in patients with both pulmonary aneurysms and deep vein thrombosis. Also, it is not stated whether to include previous thrombotic events as superficial thrombophlebitis, ICT, pulmonary embolism in the criteria for diagnosis. Addition of the ICT, especially when combined with pulmonary aneurysms, to the criteria for diagnosis of BD might alleviate this diagnostic challenge. We found 154 cases of ICT and BD published 2000 to end of 2014, additional 25 cases (1965 to 2000) were also studied in a previous report, so there are currently in the literature more than 179 cases of BD and ICT. Analysis of the data of this subgroup of patients could provide a lot of missed information.

Embolic events in BD

This review showed that 60% of patients with BD complicated by left ventricular thrombi suffered from an embolic event. The first patient (22-year-old) presented to the emergency ward with fever and neurological symptoms (hypoesthesia and slurred speech). Neurological examination revealed right facial paralysis and dysarthria. Brain imaging showed multiple acute infarcts in the right frontal, parietal, temporal, and occipital regions. Diagnosis of BD was made based on history of recurrent orogenital ulcers, cerebral, and cardiovascular involvement. Three months later and while on immunosuppressive therapy, the left ventricular thrombus disappeared and the neurological examination was unremarkable [60]. The second patient (33-year-old Tunisian) complained of shortness of breath, fever, headache, and right hemiparesis. The CT scan showed evidence of left occipito-parietal embolic lesion. The patient was operated and diagnosis of BD was made based on the presence of orogenital ulcers, neurological, and intracardiac thrombosis [63]. The third patient (13-year-old girl) had acute popliteal artery embolic occlusion and left ventricular mass. She underwent surgical removal of the left ventricular thrombus while multiple masses were additionally detected in the right ventricle, atria, and coronary sinus. The patient had additionally pulmonary aneurysm and was diagnosed as BD based on history of intermittent ulcers, pulmonary aneurysms, and cardiovascular thrombosis [36]. On the other hand, 98% of pulmonary thromboembolic events were recorded in patients with right sided thrombi. So, it seems that both the ICT and pulmonary thromboembolic events are somehow related to each other. It was previously suggested that pulmonary vascular lesions in BD are due to in-situ vasculitis rather than due to embolization whether from the heart or from the peripheral veins because the thrombi are usually tightly adherent to the underlying endothelial lining [6]. Only 25 reports commented on the mobility of the cardiac masses. 22 were mobile and 88% of them were associated with pulmonary thromboembolic findings. This particular finding should be further studied because it has important therapeutic impact. Few physicians in these reports avoided anticoagulation in patients with ICT because of fear of rupture of pulmonary aneurysm with subsequent hemoptysis and hemorrhage, the majority, however, prescribed anticoagulation (n=64). About 85% of these patients improved with the use of anticoagulation while 2 patients developed severe fatal hemoptysis [20,21,38]. Interestingly, an ICT reduced in size in a patient who received only anticoagulation without concomitant use of immunosuppressive therapy [67]. We could not ignore the mortality seen in patients receiving anticoagulation, but also we could not deny its beneficial therapeutic effect in the remaining patients. The use of anticoagulation in patients with ICT should be based on analysis of all available reports and case series to create a score system providing better choice of patients who should not receive anticoagulants without depriving the others from their therapeutic benefit.

As previously mentioned [6], the differential diagnosis of ICT was a primary cardiac tumor especially myxoma and vegetations of infective endocarditis. The clinical picture in some reports, however, simulated other diseases as tuberculosis [18], respiratory tract infection [45], myeloproliferative disease [51], other rheumatological disease, malignancies [48], and fever of unknown origin [41].

CONCLUSION

The diagnosis of BD in patients presenting with ICT is a challenging task especially for cardiologists. The early dermatological/rheumatological consultation for all patients with ICT is therefore recommended. Addition of ICT, especially when combined with pulmonary artery aneurysms, to the criteria used for diagnosis of BD might increase its sensitivity and allow earlier diagnosis of the disease. Some ICT are mobile and might be responsible for the development of pulmonary and peripheral embolic complications. The use of anticoagulation in patients with BD and ICT should be based on clear recommendations.

DISCLOSURE

The authors declare no conflicts of interst.

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