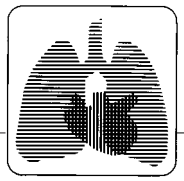

Intracardiac Thrombus in Behçet's Disease*

A Systematic Review

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Background: **Intracardiac thrombus formation is a rare but serious complication of Behçet's disease. We aimed to review the clinical and pathologic correlates of cardiac thrombus formation in the context of Behçet's disease.**

Methods and results: **A comprehensive search of the medical literature was conducted using MEDLINE including bibliographies of all selected articles. Although the disease has a unique geographic distribution, being most common in the population of the ancient Silk Route, cases complicated by intracardiac thrombus have mostly originated from the Mediterranean basin and the Middle East. Young men appear to be most at risk, with the right heart the most frequent site of involvement. The first symptoms and signs of the disease frequently precede systemic organ manifestations. In those cases in which intracardiac thrombus occurs, it is apparent in more than half of cases on first recognition of the disease.**

Conclusion: **A diagnosis of Behçet's disease should be considered if a patient presents with a mass in the right-sided cardiac chambers, even in the absence of the characteristic clinical features of the condition. This is particularly applicable if the patient is a young man from the Mediterranean basin or the Middle East.** ***(CHEST 2000; 118:479–487)***

Key words: Behçet's disease; Behçet's syndrome; cardiac involvement; cardiac thrombus

Abbreviations: ESR = erythrocyte sedimentation rate; HLA = human leukocyte antigen

Behçet's disease is a multisystemic inflammatory disease especially frequent among the Japanese and Mediterranean basin population. Its unique geographic distribution is associated with the prevalence of certain human leukocyte antigen (HLA)-B antigens, especially HLA-B5 and HLA-B51.[1] The disease is difficult to diagnose, and in the absence of a definitive diagnostic laboratory test, reliance is on characteristic clinical features. Orogenital ulceration is so constant that it is a cornerstone of the diagnosis, which can be made with increased confidence in the presence of concomitant ocular involvement, arthritis, skin lesions, CNS, or cardiac disease. The first manifestations of the disease may precede the appearance of other symptoms and signs essential for the diagnosis by many years.[2] Venous and arterial vasculitis can be demonstrated in up to one third of patients,[3] but despite the multisystem involvement, cardiac pathology has been reported relatively infrequently. Pancarditis, acute myocardial infarction, conduction system disturbances, and valvular disease have all been described.[4] Intracardiac thrombus formation is very uncommon. We conducted a cumulative literature search in which we were able to find only 24 cases previously published in 21 reports[3,5–24] in which Behçet's disease was associated with intracardiac thrombus. We reviewed the clinical and pathologic correlates of cardiac thrombus formation in the context of Behçet's disease.

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Manuscript received August 12, 1999; revision accepted November 29, 1999.

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Materials and Methods

Search Strategy

To identify the relevant literature we used computerized literature searches of the National Library of Medicine's MEDLINE from 1966 to April 1999 using the key words *Behçet's disease* or *Behçet's syndrome,* each together with *cardiac thrombus, cardiac thrombi, cardiac involvement,* or *cardiac lesion.* The searches were inclusive of all languages. Bibliographies of all articles were reviewed for other relevant articles.

Diagnostic Criteria

Diagnosis requires the presence of oral ulceration in addition to any two of four additional features[25]: genital ulceration, ocular involvement, positive pathergy test, or skin manifestations (erythema nodosum, papulopustular lesions, acneiform nodules, pseudofolliculitis). Other features not considered essential for the diagnosis, but potentially useful in an individual case, include subcutaneous thrombophlebitis, deep vein thrombosis, arterial occlusion or aneurysm, GI ulceration, epididymitis, CNS involvement, arthritis, and a family history of the condition. All included patients fulfilled the diagnostic criteria.

Patients

A total of 21 relevant articles including 24 cases were identified, of which four were written in French. We also included a 19-year-old Turkish patient as a 25th case, observed for 3 years (N.M.).

Results

Epidemiology

Of the 25 Behçet's patients with intracardiac thrombus, 21 (84%) originally came from the ancient Silk Route areas. Nineteen of these 21 patients (90%) were confined to Mediterranean basin regions or the Middle East (Turkish, 5; Arabian, 5; North African, 5; French, 2; Israeli, 1; and Sicilian, 1). The male to female ratio was 23:2, and the mean age was 28 years (range, 12 to 51 years; Table 1). Five patients with an established diagnosis of Behçet's disease were receiving specific drug therapy (prednisone, colchicine, cyclophosphamide, and indomethacin).

Presenting Clinical Features of Intracardiac Thrombus

Relationship Between Concurrent Clinical Features, Activity, and Course of Disease: Intracardiac thrombus was clearly stated to be a presenting feature in more than half (13 of 23) of the patients. However, for other patients, its detection was up to 25 years after the onset of the disease (2 months to 25 years). At the time of detection of intracardiac thrombus, fever, hemoptysis, dyspnea, and cough were the predominant symptoms (seen in 52%, 48%, 44%, and 20% of patients, respectively; Table 2). Organomegaly was present in 28% of patients. A pathergy test was stated to be positive in 11 patients and negative in 2. HLA B5/B51 positivity was noted in six of the eight patients tested. The erythrocyte sedimentation rate (ESR) had been recorded in 14 patients (Table 3): values were significantly elevated in all but one (patient 13), with an average maximum recorded ESR of 76 mm/h.

Vascular and Pulmonary Involvement: Involvement of large arteries occurred in 12 patients. In 10, this took the form of pulmonary artery aneurysm formation, either alone or in association with renal artery or aortic involvement (Table 3). Fourteen (56%) patients had venous thrombosis (Table 3). Vena cava thrombosis was observed in seven (28%). In five patients, this was located in the superior vena cava, and in two, the inferior vena cava. Two patients had superior sagittal sinus and right transverse sinus thrombosis. In two patients, thrombosis of the hepatic veins or inferior vena cava caused the Budd-Chiari syndrome (patients 15 and 25). Pulmonary thromboembolism was seen in 13 patients (52%; Table 3). In seven of these 13 (54%), thrombophlebitis was observed in the major vessels and may have been the source of the embolus. Four patients were said to have pulmonary vasculitis.

Incidence of Valvular Heart Disease and Cardiac Failure: The presence of thrombus within the right heart was associated with tricuspid valve involvement in five patients. This was the most commonly involved valve. In three patients, thrombus interfered with the functional integrity of the valve (patients 17, 22, and 25). In the other two patients, the valve leaflets were either thickened or replaced by fibrous tissue (patients 2 and 14). Five patients experienced right heart failure at some point in the clinical course: cardiac failure was unaccompanied by valvular pathology in two (patients 1 and 9).

Differential Diagnosis

The clinical presentation of intracardiac thrombus was nonspecific in the majority of patients. The most common misdiagnosis on the basis of the echocardiographic appearances was a primary cardiac tumor, this diagnosis being made initially in seven patients (Table 2). In four of these, histopathologic examination was required for the diagnosis of intracardiac thrombus, and in one (patient 7), it was inferred after resolution of a right ventricular apical mass occurred with a prolonged infusion of streptokinase (Table 4). One patient had diagnosis at necropsy (patient 17).

Table 1—*Summary of Published Behçet's Cases Complicated by Intracardiac Thrombus: Principal Clinical Features

Patient No.	Study	Ethnicity	Sex	Age, yr	Diagnostic Signs and Site of Involvement of Behçet's Disease: Oral Ulcer	Genital Ulcer	Pathergy Test	Ocular	HLA-B5/B51	Skin	Arthritis	Other	Treatment of Behçet's Disease
1	Davies[5]	West Indian	M	29	+	+	NS	+	NS	+	−	Phlebitic episodes	‡NS
2	Buge et al[6]	French	M	45	+	+	+	+	NS	−	+	—	‡Pred
3	Candan et al[7]	Turkish	M	35	+	+	+	−	NS	−	−	Pulmonary involvement	Colc, Pred
4	Augarten et al[8]	Arab	M	15	+	+	NS	−	NS	−	−	Pulmonary vasculitis	Pred
5	Lie[9]†	American	M	29	+	+	NS	−	NS	+	−	Pulmonary vasculitis	‡Indo, Colc
6	Vanhaleweyk et al[10]†	Arab	M	18	+	+	NS	−	NS	−	−	Pulmonary vasculitis	Pred, CycloP
7	El-Ramahi et al[11]	Arab	M	23	+	+	NS	−	B5	−	−	—	Pred, Aza
8	El-Ramahi et al[11]	Arab	M	18	+	+	NS	−	NS	−	−	—	Pred, CycloP
9	El-Ramahi et al[11]	Arab	M	30	+	+	NS	−	NS	+	+	—	‡NS
10	Pottiez and Francois[12]	Sicilian	F	33	+	+	NS	+	B5	−	+	—	‡NS
11	Koc et al[3]	Turkish	M	17	+	+	+	+	NS	−	+	—	‡Nil
12	Sayin et al[13]	Turkish	M	29	+	+	+	−	B5	−	−	Venous thrombi	Pred, CycloP
13	Madanat et al[14]	Chechen	M	51	+	−	+	−	NS	+	+	Arterial occlusion	‡Pred
14	Mendes et al[15]	Cape Verdean	M	29	−	+	NS	−	NS	−	−	Cardiovascular involvement	Pred, Aza
15	Islim et al[16]	Caucasian	M	32	NS	+	NS	+	NS	+	−	Malaise, weight loss	Pred, Aza
16	Nakata et al[17]	Japanese	M	12	+	+	+	−	NS	+	−	Ileal ulceration	Pred
17	Soulami et al[18]	Moroccan	M	27	+	+	+	−	NS	+	−	—	Nil
18	Huong et al[19]	French	F	32	+	+	NS	−	NS	−	+	—	Colc
19	Huong et al[19]	Algerian	M	27	+	−	NS	+	NS	−	+	—	Pred, Colc, Aza
20	Huong et al[20]	Moroccan	M	48	+	+	−	−	B5	+	−	Weight loss, phlebitis	Pred, Colc, Aza
21	Rougin et al[21]	Israeli	M	26	+	+	−	−	Neg	−	−	Vascular involvement	‡Pred
22	Kirali et al[22]	Turkish	M	28	+	+	+	−	B5	−	−	—	CyA, Pred
23	Harmouche et al[23]	Moroccan	M	28	+	+	+	−	NS	−	+	Weight loss	Pred
24	Duchene et al[24]	North African	M	14	+	+	+	+	B51	+	−	—	‡Pred, Colc
25	This study	Turkish	M	19	+	+	+	−	Neg	+	−	Pulmonary involvement	Pred, Colc, CycloP

*Aza = azathioprine; Colc = colchicine; CyA = cyclosporin; CycloP = cyclophosphamide; Indo = indomethacin; Nil = no treatment; NS = not stated; Pred = prednisone; Neg = negative.

†Patients diagnosed as having incomplete Behçet's disease in the original article.

‡Patients with a diagnosis of Behçet's disease before intracardiac thrombus.

Pathology

The exact sites of the lesions were variable. Most were in the right side of the heart. Those in the right atrium were variably attached to the free wall (patients 6, 12, and 22) or the septum (patient 12), extended into the superior (patient 12) or inferior (patient 15) venae cavae or protruded through the tricuspid valve (patient 21), and varied from small (patients 6 and 15) to massive (patient 12). Those in the right ventricle were attached to the free wall (patient 6) or the annulus of the tricuspid valve (patient 14) and again varied from small (patient 5) to massive (patient 6). There were only three reports of involvement of the left ventricle (patients 6, 8, and 18) and one of the left atrium (patient 13). Lesions were sometimes multiple in one (patient 5) or multiple chambers (patients 6 and 23).

The histologic appearances of the lesions within the chambers were usually those of an organizing thrombus (patients 11 through 14, 16, 21, 22, and 25), although sometimes there were foci of new thrombus formation (patients 12 and 22). The organizing thrombus usually contained an inflammatory cell infiltrate composed of a mixture of granulocytes and mononuclear inflammatory cells (patients 1 and 22) or predominantly lymphocytes (patient 16). The myocardium underlying the site of attachment of the thrombus was either normal (patients 6 and 21) or deeply infiltrated by inflammatory cells extending from the overlying thrombus (patient 1). Again, the inflammatory infiltrate within the myocardium varies from mixed neutrophil granulocytes and mononuclear cells (patient 1) to one consisting of lymphocytes and plasma cells admixed with histiocytes and a

Table 2—*Clinical Features at Time of Intracardiac Thrombus

Patient No.	Disease Duration	Symptoms at the Time of Intracardiac Thrombus						Presumed Diagnosis	Diagnostic Procedure
		Hemop	Fever	Dysp	Cough	Org	Other		
1	3 yr	+	+	−	−	—	Pulmonary arteritis	None	N
2	25 yr	−	−	+	−	C, H	—	None	N
3	2 mo	+	−	+	+	—	—	Myocarditis, PTE	TTE, S
4	None	+	+	−	−	Spl	Clubbing	LPD	TTE
5	6 wk	+	+	+	−	—	Malaise, pancarditis, fatigue, weight loss	Infective endocarditis	TTE, RHAC, S, N
6	None	+	+	−	−	—	Venous sinus thrombosis with papilledema	Intracardiac thrombus	TTE, MRI, B
7	None	−	+	+	+	—	Pleuritic chest pain, bilateral papilledema	Myxoma	TTE, RHAC
8	None	+	+	−	−	—	Weight loss, bilateral papilledema	Cardiac tumor	TTE, B
9	5 yr	−	−	−	−	—	Right-sided heart failure, VT, PTE	Cardiac tumor	S
10	Many years	−	−	−	−	—	Colocutaneous fistula	Intracardiac thrombus	TEE
11	5 yr	−	−	−	−	—	Oral and genital ulcerations	NS	TEE, S
12	None	+	−	−	−	—	SVCS, pericardial effusion	Myxoma	TTE, MRI, S
13	4 yr	−	−	−	−	H	Chest pain, hoarseness, claudication	Myxoma, systemic emboli	CT, TTE, S
14	None	−	+	+	+	—	Recurrent scrotal ulcers	Pneumonia, TB, endocarditis	TTE, S
15	None	−	−	−	−	H	Distended abdominal veins	Intracardiac thrombus	TTE, CT
16	None	−	+	−	−	—	—	Infective endocarditis	TTE, S
17	None	+	+	+	−	H	Pseudofollicular skin lesions	Cardiac tumor or thrombus	N
18	NS	−	−	−	−	—	Transient facial palsy and aphasia	NS	TTE, S
19	NS	−	−	+	−	—	SVCS	NS	TTE, CT, MRI, S
20	None	+	+	−	−	—	None	Intracardiac thrombus	TTE, CT
21	None	+	+	+	+	Spl	Chest pain, weight loss	Infectious or LPD	TTE, S
22	1st none 2nd 2 yr later	−	−	+	−	—	Neck swelling, limitation in daily activities	Intracardiac thrombus	TTE, CT, MRI, S
23	6 mo	+	−	+	−	—	Weight loss	Intracardiac thrombus	TTE-TEE, RHAC
24	2 yr	−	+	−	−	—	Chest pain	Intracardiac thrombus	TEE, MRI
25	None	+	+	+	+	C, Spl, H	Skin lesions, chest pain	Stevens-Johnson syndrome, myxoma	TTE-TEE, S

*BD = Behçet's disease; B = biopsy; C = cardiomegaly; Dysp = dyspnea; H = hepatomegaly; Hemop = hemoptysis; LPD = lymphoproliferative disease; N = necropsy; Org = organomegaly; PTE = pulmonary thromboembolism; RHAC = right heart angiocardiogram; Spl = splenomegaly; S = surgery; SVCS = superior vena cava syndrome; TEE = transesophageal echocardiography; TTE = transthoracic echocardiography; TB = tuberculosis; VT = venous thrombosis. See Table 1 for other abbreviations.

†Disease duration denotes interval between recognition of Behçet's disease and presentation with intracardiac thrombus.

small number of eosinophils (patient 5). There was sometimes marked myocardial fibrosis (patient 19), which in some cases incorporated the valve leaflets (patients 2 and 19), and calcification occurred within the fibrous tissue in one case (patient 18).

Diagnostic Modality

Intracardiac thrombus was detected in three patients at necropsy and in one additional patient intraoperatively (Table 2). In all remaining patients, two-dimensional echocardiography was used at some point during investigation. This technique accurately determined the involved cavity and often it was possible to ascertain the site of attachment of the thrombus and nature of any associated disease. A transesophageal study was used in five cases (patients 10, 11, 23, 24, and 25). Other imaging modalities including CT scan and MRI were used less frequently. Cineangiography of the right heart was used in three cases (patients 5, 7, and 23).

Treatment, Clinical Course, and Outcome

Surgery, performed in nine patients for exploratory reasons, was the first attempted treatment modality in 12 patients (Table 5). Surgery was unsuccessful in four patients. In one, the mass was found to be infiltrating extensively and was not completely resectable (patient 12). Subsequent

Table 3—*Associated Clinical Features at Time of Intracardiac Thrombus or During Follow-up

Patient No.	VT	PTE	ESR, mm/h	Other Involvement
1	Present	Present	67	Skin, ocular, widespread thrombovasculitis, PAAs, pulmonary vasculitis
2	Present	Absent	32–55	CNS, SVC thrombosis, joint
3	Absent	Present	29–53	Pulmonary
4	Absent	Absent	90–100	PAA
5	Present	Present	68	PAAs, pulmonary thromboangiitis, superficial VT
6	Present	Absent	NS	PAA, superior sagittal and right transverse sinus thrombosis
7	Absent	Present	116	Pulmonary vasculitis, occlusive arteritis
8	Present	Present	140	Pulmonary vasculitis, superior sagittal and right transverse sinus thrombosis
9	Present	Present	NS	Skin, joint, deep VT
10	Absent	Pbsent	NS	GI
11	Present	Absent	NS	Ocular and joint involvement, SVC thrombosis
12	Present	Absent	NS	PAAs, SVC thrombosis
13	Absent	Absent	10	Ulceration of mitral valve leaflets, endocarditis, major arterial occlusion
14	Present	Present	NS	PAA, SVC thrombus
15	Present	Absent	NS	Budd-Chiari syndrome, IVC obstruction
16	Absent	1st, absent 2nd, present	50	Skin, GI
17	Absent	Present	NS	Skin
18	Absent	Absent	NS	Mitral valve prolapse, joint
19	Present	Absent	NS	SVC thrombosis, joint
20	Present	Present	80	PAA, femoro-popliteo-tibial thrombophlebitis
21	Absent	Present	87	Bilateral renal artery stenosis, PAAs, APA
22	Present	Absent	33	IVC thrombus
23	Absent	Absent	60	PAA
24	Absent	Present	NS	PAA, skin
25	Present	Present	80	Pulmonary, skin, hepatic veins thrombus (Budd-Chiari syndrome)

*APA = aortic pseudoaneurysm; IVC = inferior vena cava; PAA(s) = pulmonary artery aneurysm(s); SVC = superior vena cava. See Tables 1 and 2 for other abbreviations.

treatment with prednisone and cyclophosphamide was unsuccessful, and the patient died after a massive hemoptysis from a ruptured pulmonary artery aneurysm. Three other patients died postoperatively. The cause in two was uncontrollable bleeding from the pulmonary vasculature. One died of unknown reasons (patient 9). Five of the six survivors remained well at follow-up, and one (patient 16) had two recurrences of intracardiac thrombus after initial surgery and remained stable on warfarin after the second surgical procedure. Two of the 11 patients treated surgically were lost to follow-up.

Anticoagulant or thrombolytic therapy was the first-line treatment in eight patients. In seven, this was associated with complete resolution of intracardiac thrombus, with recurrence in one patient at 2 years (patient 22; initial treatment had included immunosuppressive therapy). Two patients were treated with prednisone alone, with resolution of symptoms, but the outcomes were not recorded (patients 4 and 23). Three patients received no specific therapy for intracardiac thrombus because it was recognized only at autopsy. The reasons for death in this group were infection, massive hemoptysis, and pulmonary thromboembolism.

Discussion

Although Behçet's disease is found in a broad geographic band stretching from the Mediterranean basin to the Far East, Behçet's disease complicated by intracardiac thrombus seems to be confined predominantly to patients from the Mediterranean basin and the Middle East. This mostly includes inhabitants of the old greater Ottoman Empire that extended well into the Balkans and across the Mediterranean littoral areas, where the incidence and prevalence still far exceed those elsewhere. It is well

Table 4—*Pathology of Intracardiac Thrombus

Patient No.	Source of Histologic Material	Involved Cavity	Histologic Description of Mass	Histologic Description of Myocardium
1	Necropsy	RV	Thrombus	Endomyocarditis and granulation tissue
2	Necropsy	RA, RV	Old thrombus	Massive endocardial fibrosis
3	Surgery	RV	Organized thrombus	Endocarditis
4	No biopsy	RV		
5	Surgery and necropsy	RV	Thrombus	Pancarditis with fibrosis
6	Biopsy	RA, RV, LV	Thrombus	Normal
7	No biopsy	RV	—	—
8	Biopsy	RV, LV	Thrombus	NS
9	Surgery	RV	Thrombus	Endomyocardial fibrosis
10	No biopsy	RV	—	—
11	Surgery	RV	Organizing thrombus	NS
12	Surgery	RA, SVC	Organized and new thrombus	NS
13	Surgery	LA	Inflamed organized thrombus	NS
14	Surgery	RV	Organized thrombus	Granulation tissue
15	No biopsy	RA	—	—
16	1st episode; surgery	RA	Inflamed organized thrombus	Endocarditis
	2nd episode; surgery	RA, main PA	Inflamed organized thrombus	
	3rd episode; no biopsy	RA, main PA	—	
17	Necropsy	RV	Inflammatory vegetation with Lymphohistiocytic infiltrate	Endomyocardial fibrosis
18	Surgery	LV	Mural thrombus	Ulcerated endocarditis
19	Surgery	RV	Mural thrombus	Endomyocardial fibrosis
20	No biopsy	RV	—	—
21	Surgery	RA (prolapsing into RV)	Organized thrombus	No inflammation or fibrosis
22	Surgery	RA (prolapsing into RV)	Organized and new thrombus	NS
23	No biopsy	RA (prolapsing into RV), RV	—	—
24	No biopsy	RV (mobile)	—	—
25	Surgery	RA (prolapsing into RV)	Organized thrombus	—

*LV = left ventricle; PA = pulmonary artery; RA = right atrium; RV = right ventricle. See Tables 1, 2, and 3 for other abbreviations.

recognized that GI involvement in Behçet's disease is common in Japan but rare in Turkey[26]; conversely we have found only one case complicated by intracardiac thrombus among Far Eastern patients. This is consistent with the geographic variability in mode of clinical presentation and systemic organ involvement, suggesting that genetic predisposition may be highly relevant in determining systemic organ involvement in the disease.[27,28] There is evidence from heat shock protein studies for the implication of infective agents in Behçet's disease.[29] That the susceptibility of a certain population to this rare complication could be attributable to the variation in the presence of environmental factors, such as bacterial or viral agents (possibly mediated by meteorologic factors), is an attractive hypothesis.

In considering the full clinical spectrum of the disease, we found that women are far outnumbered by men. In severe disease, such as ocular, pulmonary arterial, and CNS involvement, this is particularly noticeable.[30] We have found a similar pattern in cases complicated by intracardiac thrombus, with a very marked predominance of men (only two cases occurring in women). Notably, even conditions exhibiting estrogen dependence, such as thrombophlebitis, are predominantly encountered in men with Behçet's disease rather than women.[30] The severe systemic manifestations also affect a younger age group.[31] We have found intracardiac thrombus to be more common in young patients with the condition. The classic features of Behçet's disease usually emerge in the third decade,[31] but 29% of patients with intracardiac thrombus presented in the second decade.

There is a considerable body of knowledge about the presence of autoreactive antibodies against oral mucosa in Behçet's patients.[32,33] Antiphospholipid antibodies have been identified in one patient with Behçet's disease and intracardiac thrombi: a causative role has been suggested (patient 23). Anti-endothelial cell antibodies have been associated with vascular involvement.[34] However, there is no published evidence specific to intracardiac thrombosis. It is not known whether the anti-endothelial cell antibodies are also directed against antigens presented by endocardial cells.

Some of the manifestations of Behçet's disease have been considered to result from neutrophil hyperactivity.[35] Increased chemotaxis, active oxygen overproduction, and increased endothelial cytotoxic-

Table 5—*Cardiologic Sequel and Outcome

Patient No.	Valve Involvement	Cardiac Failure	Recurrence of ICT (time)	Treatment of ICT	Outcome
1	Absent	Present	Absent	None (autopsy finding)	Died of massive hemoptysis
2	Tricuspid	Present	Absent	None (autopsy finding)	Died of infection
3	Tricuspid	Absent	Absent	Surgical removal	Discharged in good health on oral anticoagulants and IST
4	Absent	Absent	Absent	Prednisolone	Resolution of symptoms, outcome of ICT not defined
5	Absent	Absent	Absent	Surgical removal	Died of fatal hemoptysis from ruptured PAA
6	Absent	Absent	Absent	Heparin, prednisone, cyclophosphamide	Mural thrombi gradually resolved with anticoagulants, corticosteroids, and cyclophosphamide
7	Absent	Absent	Absent	Heparin, streptokinase	Almost complete resolution of thrombus
8	Absent	Absent	Absent	Heparin	Resolution of thrombus and symptoms
9	Absent	Present	Absent	Surgical removal	Died in early postoperative period
10	Tricuspid	Absent	Absent	Heparin	Thrombus resolved in 3 mo
11	NS	NS	NS	Surgical removal	Not defined
12	Absent	Absent	Absent	Incomplete surgical removal, prednisone, cyclophosphamide	Died of massive hemoptysis during emergency surgery
13	Mitral	Absent	Absent	Surgical removal	NS after postoperative recovery
14	Tricuspid	Absent	Present	Surgical removal	Complete resolution of symptoms with warfarin
15	Absent	Absent	Absent	Warfarin, IST	ICT resolved by 18 mo
16	Absent	Absent	Present 2nd (4 wk) 3rd (7 wk)	1st, surgical removal 2nd, surgical removal 3rd, prednisone, LMWH	ICT had recurred on two occasions, stable with warfarin
17	Tricuspid	Present	NS	None (autopsy finding)	Died of massive PTE
18	Mitral	Absent	Absent	Surgical removal	Resolution of symptoms
19	Tricuspid	Present	Absent	Surgical removal followed by anticoagulant, IST	Lost to follow-up
20	Absent	Absent	Absent	Aspirin, IST	Symptoms and mass resolved in 6 mo
21	Aortic	Absent	Absent	Surgical removal	Died from massive bleeding from ruptured ascending APA postoperatively
22	Tricuspid	1st, absent	Present	1st, anticoagulant, IST	ICT recurred after 2 yr following successful medical treatment, second thrombus successfully surgically removed
		2nd, present	2nd (2 yr)	2nd, surgical removal	
23	Absent	Absent	Absent	Prednisone	Static for 12 mo and then lost to follow-up
24	Absent	Absent	Absent	Prednisone, anticoagulant, IST	After 13 mo asymptomatic and the lesion disappeared
25	Tricuspid	Present	Absent	Surgical removal	Successfully surgically removed, stable with IST

*ICT = intracardiac thrombus; IST = immunosuppressive therapy; LMWH = low molecular weight heparin. See Tables 1, 2, and 3 for other abbreviations.

ity have been implicated. Although the histologic descriptions of both the thrombi and the myocardium show some variation, mononuclear inflammatory cells, rather than neutrophils, predominate. The exact composition of the inflammatory infiltrate may be dependent on the timing of the biopsy.

Intracardiac thrombus is uniformly associated with an elevated ESR but it is recognized that this is a poor indicator of disease activity. Plasma endothelin-1 levels appear to correlate better.[36]

The reason for the propensity to right-sided intracardiac thrombus in Behçet's disease is still unclear. On the basis of autopsy findings, it could be postulated that endomyocardial fibrosis has a role in the development of intracardiac thrombus in some patients. However, it is difficult to know whether the thrombi are secondary to underlying endocarditis or endomyocardial fibrosis, since some case reports describe normal underlying myocardium. Comparison with the endomyocardial fibrosis seen in both hypereosinophilic syndrome and carcinoid syndrome has been made,[18] but in these conditions, the valves are rarely involved. The right-sided predominance of cardiac disease in carcinoid syndrome is explained by the presence of metastatic carcinoid in the liver and the greater exposure of the right heart to serotonin, which is cleared in the pulmonary circulation. Hypereosinophilic syndrome affects both ventricles equally.

It is well established that Behçet's disease predisposes strongly to venous and arterial thrombosis (present in up to one third of cases), and elevated von Willebrand factor antigen levels have recently been demonstrated.[37] Recurrent superficial and deep thrombophlebitis of the lower extremities are the most common abnormalities, followed by vena

cava thrombosis, which was observed in six patients in this series. However, 6 of the 12 patients who had pulmonary arterial thrombosis were free of peripheral thrombus. In those patients with intracardiac thrombus, there is tight attachment of the thrombus to the endocardium or myocardium. For this reason, thromboembolism from a cardiac cavity has previously been deemed to be relatively uncommon.[3] Moreover, in some patients, the pulmonary abnormalities were seen to resolve after administration of immunosuppressive treatment rather than anticoagulation.[7,10,11] It is, therefore, possible that the pulmonary involvement is a result of *in situ* pulmonary pathology rather than embolization from a systemic vein. The lack of a clear understanding into the pathophysiology of pulmonary involvement has frequently hindered the interpretation of pulmonary perfusion defects in this condition.

The diagnosis of intracardiac thrombus is difficult in the context of the nonspecific clinical features of pyrexia and malaise, these symptoms commonly being attributed to endocarditis. The echocardiographic appearances are easily confused with those of large vegetation or more frequently with an intracardiac tumor. The differentiation from atrial myxoma is made more difficult by the fact that the appearances of a right atrial myxoma may be atypical and the surface may be covered by thrombus. In the absence of Behçet's disease, intracardiac thrombus is often found to overlie an akinetic myocardial segment.[38] However, right ventricular dysfunction was not always present in our series, and in patients with a right atrial thrombus, it was often seen to prolapse through the tricuspid valve into the right ventricle. Usually, the mass is relatively immobile, with a broad-based attachment. Transthoracic imaging may fail to determine the site of endocardial attachment, and a transesophageal study is more likely to accurately demonstrate anatomic relationships. Both intracardiac thrombus and cardiac tumors can give rise to pulmonary embolic phenomena, the latter causing right heart failure.[39]

Conclusion

Behçet's disease complicated by intracardiac thrombus most commonly occurs in the Mediterranean basin and Middle East, in young men. It usually involves the right side of the heart and often precedes other manifestations of Behçet's disease. There is frequently coexistence of cardiac and pulmonary complications, the latter commonly being responsible for death. The management of intracardiac thrombus has varied, the aim being to eradicate the thrombus and prevent recurrence. Surgical removal has the advantage of providing material for histologic examination and verification of the diagnosis. However, in the small number of cases in the published literature, medical management has been associated with a better outcome. Irrespective of the mode of management, the presence of intracardiac thrombus confers a poor prognosis, with many fatalities in these young patients.

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