



## Intracardiac thrombosis in a case of Behçet's disease associated with the prothrombin 20210G-A mutation

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### ABSTRACT

Thrombosis occurs in 20 to 30% of patients with Behçet's disease (BD), but the precise pathogenic mechanism underlying the thrombotic tendency in these patients is not well known. Venous thromboses are commonly located in the lower extremities, but right intracardiac thrombi are extremely rare. We report for the first time on a young patient with BD associated the 20210G-A prothrombin gene mutation and right intracardiac thrombosis. We suggest that the association of BD with this newly recognized prothrombotic genetic mutation may have contributed to the development of the thrombotic event in this patient.

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Key words: Behçet's disease, intracardiac thrombosis, prothrombin 20210G-A

Behçet's disease (BD) is a chronic relapsing systemic vasculitis in which recurrent orogenital ulceration is a prominent feature.<sup>1</sup> Although vascular involvement, mainly venous thrombosis, is a common complication of this disease, intracardiac thrombi are extremely rare.<sup>2</sup> While the precise pathogenic mechanism underlying the thrombotic tendency in BD is not well known, several hemostatic abnormalities consisting of endothelial dysfunction, hypofibrinolysis, plasma hypercoagulability and increased eicosanoids<sup>3-7</sup> have been reported. However, none of them has been consistently and clearly related to the thrombotic events. Therefore, there could be other causes of thrombotic risk in BD that have not yet been identified. Recent studies suggest that the presence of factor V Leiden may contribute to the risk of venous thromboembolic events in these patients.<sup>8-10</sup> Moreover, a new hereditary factor that increases thrombotic risk, prothrombin 20210 G-A,<sup>11</sup> has recently been found, but an association between this genetic mutation and BD has not yet been reported. Although vascular involvement in BD

mainly affects the venous system, venous thromboses are located principally in the lower extremities and inferior vena cava.<sup>2</sup> Thrombosis in the intracardiac area is rare, and the literature reviewed for this study contained only eleven such cases well-documented.<sup>12-22</sup> In the following report we describe for the first time a patient with right heart thrombosis associated with a molecular mutation of prothrombin 20210 G-A.

### Case Report

#### Clinical features

A 16-year old Caucasian male, with a right ventricular and right atrial thrombosis was referred to our hospital. He had a history of oral aphthosis. His health had been good until one month earlier, when fever, dyspnea and hemoptysis developed. The chest radiograph revealed no abnormalities, and cultures of sputum specimens were negative. Blood cultures were also negative. In the following days, these symptoms worsened. Fever persisted, the patient developed chest pain, and hemoptysis increased in frequency and severity. A bronchoscopic examination was not diagnostic. A computed tomographic scan of the chest was performed and a mass in the right ventricle that extended to the right atrium and inferior vena cava was detected. The following day, the patient was referred to our hospital. On physical examination, the patient appeared ill; his temperature was 39°C, blood pressure was 100/70 mmHg, and he had a smooth liver enlargement of 4 cm.

#### Biochemical and hematologic findings

The levels of urea nitrogen, creatinine, bilirubin, albumin and electrolytes were normal. The hematocrit was 31%; the blood white cell count was  $9.4 \times 10^9/L$ ; the platelet count was  $164 \times 10^9/L$ ; the mean red cell volume was 81.2 fL; the erythrocyte sedimentation rate was 43 mm; C-reactive protein was 25.5 mg/L. A test for antinuclear antibodies and antiphospholipid antibodies was negative. Homocysteine levels were normal, as were the other laboratory tests.

#### Radiological findings

Transesophageal echocardiography: showed a round mass in the right ventricle of  $40 \times 21$  mm, and another one in the right atrium (Figure 1). Magnet-

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Figure 1. Transesophageal echocardiography: Image of the thrombus in the right ventricle.



Figure 2. Magnetic resonance angiography. Right atrial and right ventricular thrombosis.

ic resonance angiography of the chest and abdomen: revealed some perfusion defects in the lungs, a mass in the heart, and some filling defects and enlargement of the inferior vena cava suggesting thrombosis (Figure 2).

#### Diagnosis and follow-up

These findings raised suspicions that warranted a biopsy of the mass, especially in view of the clinical worsening. A surgical procedure with thoracotomy and resection of the mass under cardiopulmonary bypass was performed, and the histologic study gave a diagnosis of organized thrombus. Cultures of the specimen were all negative.

After surgery, anticoagulant therapy with low molecular weight heparin was started. Behçet's disease was suspected, even though the pathergy test was negative, and corticosteroid treatment was started with methyl-prednisolone 1 mg/kg per day. In the following days, the patient improved dramatically, and fever disappeared, as did the other symptoms. No surgical complication appeared. Ten days after

Table 1. Coagulation and thrombophilic findings in the propositus.

Test	Propositus	Normal values
PT(s)	13.3	11.5-13.7
APTT (s)	27.7	26.0-37.0
Fibrinogen (mg/dL)	274	170-400
Factor II act (%)	107	70-120
Factor VII act (%)	80	70-120
Factor VIII:C (%)	288	70-120
vWF: (Ag) (%)	279	48-140
Factor IX act(%)	77	70-120
Factor X act (%)	121	70-120
Plasminogen (%)	70	70-120
PAI-1 (ng/mL)	52.37	2.00-30.00
TAT (ng/mL)	1.30	1.00-4.10
F 1+2 (nmol/L)	0.32	0.80-1.20
Lupus anticoagulant	negative	
aCL IgG (GPL)	4	0.0-15.0
aCL IgM (MPL)	5	0.0-13.0
ATIII (%)	90	70-120
PC (%)	84	70-120
PS (%)	80	60-120
HCo II (%)	89	66-126
APC-R	2.8	> 2
Factor V Leiden	negative	
20210G-A	positive	

PT: prothrombin time; APTT: activated partial thromboplastin time; TT: thrombin time; vWF: von Willebrand factor; PAI-1: plasminogen activator inhibitor-1; TAT: thrombin-antithrombin III complex; F 1+2: prothrombin fragment 1+2; aCL: anticardiolipin antibodies; ATIII: antithrombin III; PC: protein C; PS: protein S; HCo II: heparin cofactor II; APC-R: activated protein C ratio.

surgery, an echocardiography was performed, and a new thrombus in the right ventricle appeared in spite of the patient being under treatment with low molecular weight heparin at therapeutic doses. There were no findings in the right atrium. During these days a scrotal ulcer appeared, which added strength to our diagnosis. We started treatment with azathioprine at a dose of 2 mg/kg/day and maintained the anticoagulant and corticosteroid therapy. The patient was asymptomatic during the following days and on the 25<sup>th</sup> day was discharged.

#### Hemostatic and thrombophilic tests

Three months later and after low molecular weight heparin had been suspended for 24h to avoid its possible effects on certain hemostatic parameters, coagulation studies were performed (Table 1). The only abnormal findings were increased factor VIII coagulant (288%; normal range 70-120%); increased antigenic von Willebrand factor (279%; normal range 48-140%) and PAI-1 (52.37 ng/mL; normal range 2.00-30.00 ng/mL). In addition, a prothrombin 20210G-A mutation was found. A family study was carried out and showed that the patient's mother and sister and two of his maternal uncles were also heterozygous for the genetic mutation, although they had never suffered thrombotic events.

## Discussion

Vascular involvement is frequent in BD, and has been reported to occur in one-third of patients.<sup>2</sup> Venous lesions are the most common abnormality and usually consist of recurrent superficial and deep vein thromboses, most often involving the lower extremities.<sup>2,23</sup> Thrombosis of the vena cava is the second most common vascular lesion, but intracardiac thrombosis in the right ventricle is extremely rare. In a series of 137 BD patients only one case of intracardiac thrombus within the right ventricle was described.<sup>2</sup> The literature consulted for this study contained only eleven<sup>12-22</sup> well-documented cases of intracardiac thrombosis associated with BD, although the possible thrombogenic mechanisms were scarcely dealt with.

Because of the vasculitis that affects many of these patients, an increase in endothelial activation markers<sup>3-5</sup> can be detected. Such was the case in our patient, who showed increases in clotting factor VIII, antigenic von Willebrand factor and PAI-1. The plasma hypercoagulability markers, such as thrombin-antithrombin complex and prothrombin fragments 1+2,<sup>8</sup> that are often found in these patients were not observed in our patient.

It has been suggested that one of the causes of thrombotic events in patients with BD is the presence of hereditary thrombotic risk factors, such as PC and PS deficiencies,<sup>24-26</sup> but the levels of these inhibitors e.g. ATIII in our patient were normal and in agreement with those reported by other authors.<sup>27,28</sup> However, a recent report suggested that an association between BD and factor V Leiden markedly increases the risk of thrombosis, even as much as 6 fold.<sup>8</sup>

More recently prothrombin 20210G-A has been described as another hereditary thrombotic risk factor. This genetic prothrombin mutation is associated with high levels of circulating prothrombin, which induces an approximately three-fold increase in thrombotic risk.<sup>11</sup>

Our patient, like his mother and sister, has this prothrombin mutation, and this may have triggered the development of thrombosis at an earlier age than in most cases of intracardiac thrombosis reported in BD patients.<sup>12,15-22</sup>

To our knowledge this is the first report of BD associated with 20210G-A prothrombin mutation and, in addition, with this very unusual intracardiac thrombotic localization. Given the high prevalence of this mutation in the healthy southern Europe population,<sup>29</sup> the association of this genetic mutation in our patient is not surprising. Further studies are needed to determine the prevalence of this genetic prothrombotic factor in BD and whether it constitutes a major risk factor in the development of thrombotic events in patients with this disease.

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*AV and MJF: diagnosis and therapy, co-ordination of research studies and writing the article; PV, YM and FF: hemostatic and coagulation studies; AE: genetic studies of factor V Leiden and 20210G-A prothrombin mutation; VO and MJGF: clinical care of the patient; JA: revision of the paper and final approval.*

## Disclosures

*Conflict of interest: none.*

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