Intra-cardiac thrombi: Behçet's disease?

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Keywords

Behçet's disease; thromboembolic events; heart diseases; anticoagulants; child.

Abstract

We report the case of a 6 years old male child presenting with deep vein thrombosis and intra-cardiac thrombi. Despite anticoagulation treatment, the thrombi progressed leading to cardiovascular failure requiring a surgical approach. The initial clinical presentation, unusual progression and exclusion of differential diagnoses, guided to the suspicion of Behçet's disease. The patient developed new symptoms and responded to anti-inflammatory and immunosuppressive treatments supporting this diagnosis. Behçet's syndrome is a systemic inflammatory disease whose incidence in the paediatric population and aetiology are still unknown. Furthermore there are no evidenced-based treatment guidelines.

Introduction

Behçet's disease (BD) is a chronic autoinflammatory condition. The disease is rare in paediatrics and the incidence is unknown (1). The diagnosis is clinical and no laboratory test can confirm it. The international criteria for BD furnish a clinical score as a guide for diagnosis and classification (2). It can affect different organs, but cardiac presentation is uncommon. Intracardiac thrombus is even more rare (3). We present the case of a child with a catastrophic evolution of deep vein thrombosis and intra-cardiac thrombi formation. Due to progression despite correct anticoagulation treatment, BD was suspected and a treatment with immunosuppressive and anti-inflammatory agents was started.

Clinical case

A 6 year-old previously healthy male child presented with a two-day history of fever and sudden collapse while walking, with complete recovery within one minute. The patient, of Moroccan origin, was born in Europe. In his medical history, the parents reported a severe coronavirus (SARS-CoV-2) related acute respiratory distress syndrome 13 months previously.

The initial physical examination was unremarkable. The patient's vital signs were: oxygen saturation 100% - respiratory rate 41 breaths per minute – arterial blood pressure 100/68 (79) mmHg– heart rate 145 beats per minute – temperature 36.6 °C. Laboratory tests showed moderate inflammation (white blood cells 11010/mm3 [N 7800-13500], C-reactive protein 120 mg/L [N ≤ 5mg/L], erythrocyte sedimentation rate 80 mm/h [N ≤ 20 mm/h]). His electrocardiogram and chest radiograph showed no abnormalities. The patient was admitted for monitoring.

The evolution was marked by left leg pain and swelling. Echography confirmed a partial venous thrombus extending from the common femoral vein to the external iliac vein. Basic coagulation tests were normal. Taking into consideration the young age of the patient and the transient loss of consciousness, a chest computed tomography (CT) was performed showing a massive truncal pulmonary embolism. The patient was started on anticoagulant (intravenous heparin infusion) and antibiotic (ceftriaxone) therapy and transferred to the Paediatric Intensive Care Unit.

The evolution was characterized by progression of the thrombus towards the inferior vena cava (IVC), appearance of intra-cardiac thrombus (ICT) (right atrium (RA) and right ventricle (RV)) and clinical deterioration despite adequate anticoagulation (Figure 1A-1B). On day 9 of admission, he developed his first episode of acute cardiovascular failure due to a thrombus in the RV. He underwent a surgical removal

Figure 1A. Transthoracic echocardiogram (TTE) - short axis- showing a thrombus in the common trunk pulmonary artery (blue arrow mark).

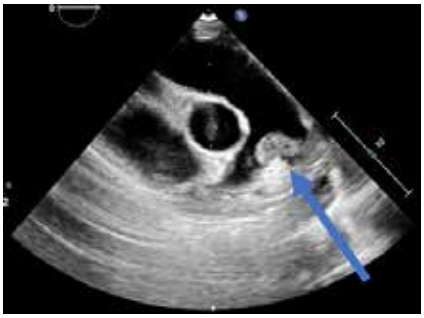


Figure 1B. Transthoracic echocardiogram (TTE) showing the right ventricular (RV) thrombus (blue arrow mark).

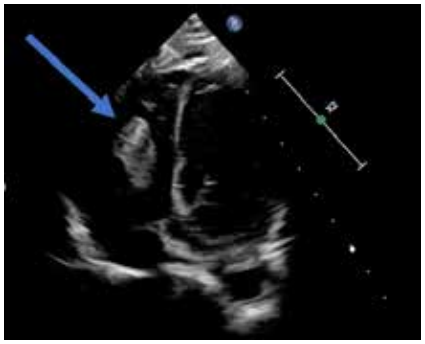


Figure 1C. Computed tomography showing thromboses of the upper vena system.

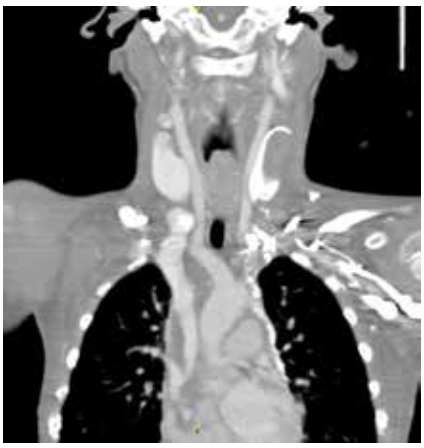
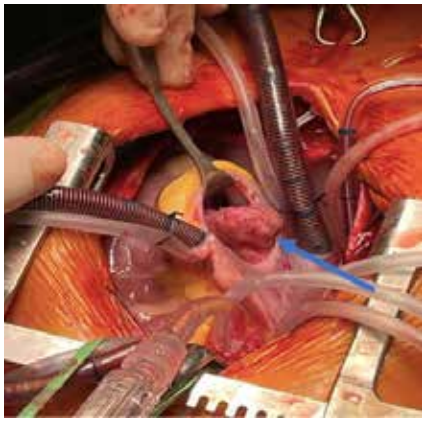


Figure 2. Perioperative aspect of the main pulmonary artery thrombus: irregular, smooth, hard mass adherent to the endothelium (blue arrow mark).



of this right heart thrombus (Figure 2). Two days later, he developed a thrombus in the right atrium with hemodynamic intolerance.

More in-depth assessments were considered and diagnostic tests were performed to confirm or exclude possible disorders that could have caused a similar clinical presentation (Table 1). The hypothesis of a BD associated with ICT and extensive pulmonary embolism was suggested. Other possible pathologies leading to rapid formation of ICT were heparin-induced thrombocytopenia (HIT) or diffuse thrombosis due to SARS-CoV-2 infection. As shown in table 1, the platelet factor 4 (PF4)/ heparin antibodies were negative, thus excluding the diagnosis of HIT. Three polymerase chain reaction (PCR) tests for SARS-Cov-2 were negative during hospitalization.

To support the diagnosis of BD, we screened for HLA-B51 and performed an ophthalmoscopic evaluation and a pathergy test. The three tests were negative not supporting the diagnosis of BD.

Coagulation tests showed that protein S was on the low limit and the patient's mother had a protein S deficiency (Table 1). However, these tests were not conclusive for diagnosis.

The thrombi were rapidly extensive. On day 12 of admission, the patient developed a superior vena cava syndrome. A CT angiogram showed that the thrombus extended from the superior vena cava to the RA. The superior vena cava network was completely thrombosed. On the left side, the thrombus extended to the internal jugular vein, subclavian vein (partial) and brachiocephalic vein (complete). On the right side, the subclavian vein was patent, but the internal jugular vein and the brachiocephalic veins were thrombosed (Figure 1C).

Given the acute severity of the disease, the patient was started on aggressive anti-inflammatory and immunosuppressive therapies. We started with corticosteroids (pulses of methylprednisolone 15mg/kg/day for three days, followed by methylprednisolone 2 mg/kg/day), anti-tumour necrosis factor (TNF)-alpha (5mg/kg, on week 0 – week 1 – week 4) and azathioprine (2mg/kg/day). Almost simultaneously the anticoagulant therapy was switched to antiaggregating therapy. Despite medical treatment the patient's condition was life threatening on three occasions (day 9, 13 and 20) and a multidisciplinary decision was made to proceed three times with surgical thrombectomy under extracorporeal circulation (Figure 2) and IVC ligation.

The clinical evolution was slowly favourable and the inflammatory syndrome decreased. He was finally discharged on day 53, treated with corticosteroids, azathioprine and acenocoumarol, with follow-up

Table 1: Differential diagnosis with pertinent results of findings.

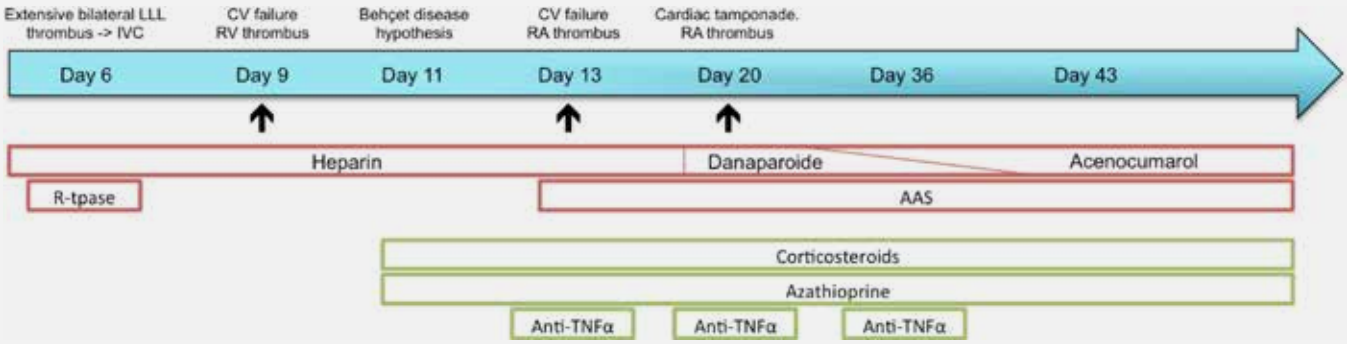
Sars-CoV2 : severe acute respiratory syndrome coronavirus 2 ; PCR: polymerase chain reaction ; PF4/heparin: platelet factor 4/heparin ; HLA B51 : human leukocyte antigen class I, B, 51 ; CT scan : computed tomography scanner ; Whole-body PET CT: whole body positron emission tomography computed tomography.

Causes	Analyses	Results
Coagulation disorder	Patient Mother of the patient	Protein S on lower limit: 65% (68-139%) Protein S deficiency: 45% (60-114%)
Infectious	Inflammatory markers SARS-CoV-2 • PCR tests during hospitalizations • Serology for vaccine induced antibodies	 Negative Positive
Genetic	Prothrombin gene mutation G20210A	No mutation
Iatrogenic	PF4/heparin antibodies	Negative
Systemic	Pathergy test HLA type Ophthalmoscopic evaluation	Negative HLA B51 negative No signs of uveitis
Tumoral	Medullary karyotype Chest CT scan Abdominal echography Whole-body PET CT	Karyotype normal 46,XY No tumour No tumour No tumour

Table 2: Timeline of the evolution of the case depicting the main events, including symptoms and management

LLL: left lower limb; IVC: inferior vena cava; CV failure: cardiovascular failure; RV: right ventricular; RA: right atrial; Anti-TNFα: tumor necrosis factor alpha inhibitors.

The arrows point out the 3 heart surgeries.



by the rheumatology, haematology and cardiology team. At the time of discharge, the diagnosis was uncertain. Our hypothesis was a BD combined with an underlying pro-inflammatory state due to a protein S level on the lower limit.

In July 2022, he had a chest CT which showed no thoracic thrombosis. In September 2022, his mother reported a few mouth ulcers and a penile ulcer, which supports the diagnosis of BD. He continues to be followed closely by a multidisciplinary team.

Discussion

The incidence of Behçet's disease in children is unknown. The average age for the early symptoms in the paediatric population is 8 years old, and the diagnosis is usually made at a later stage (6 years later) (1). This disease affects both genders but severe cases are more common in men than women (1). In a literature review evaluating patients with BD and ICT, Aksu described that there is a male predominance (87%), and thrombi affect mostly the right side of the heart (95%) (3).

The pathology is usually characterized by recurrent aphthous stomatitis, genital ulceration, arthralgia and uveitis (1). It can affect multiple systems and cardiac involvement is very uncommon (1-5%). Pericarditis, myocardial infarction, conduction abnormalities and, very rarely, ICT can be observed. Pulmonary aneurysm and thrombus may also occur (3). In case of vascular complications, venous involvement is more common (nearly 30% of patients) than arterial involvement (5-10% of patients) (1). The prevalence of cardiovascular involvement varies by country. However, ICT is one of the most recognized cardiac presentations in Mediterranean young patients and can precede the diagnosis, as in the present case (3).

The underlying mechanism for thrombosis in this disease remains unclear. One hypothesis is endothelial cell ischaemia and disruption leading to the presence of abundant inflammatory cells and platelet aggregation (4). The thrombi are usually tightly adherent to the vessel wall and have a different consistency from classic thrombi (Figure 2), making the embolization difficult (5,6). They can be confused with embolisms, although in this case the size of the ICT and the rapidity of evolution suggested in situ thrombus formation (6).

Our patient had a delayed diagnosis due to the uncommon initial presentation (thrombosis, ICT) and the lack of more international BD criteria, as described in literature (9,10). Only the development of new symptoms over time (ulcers) and the favourable evolution under anti-inflammatory and immunosuppressive treatment allowed recently to confirm the diagnosis. During his admission, other differential diagnoses were ruled out, mainly heparin-induced thrombocytopenia (HIT). Since the thrombi evolved despite standard therapeutic anticoagulation, heparin was switched to danaparoid and acenocoumarol (Table 2). The PF4/heparin complex turned out to be negative, and HIT was excluded.

High clinical suspicion remains the key for early diagnosis of BD. Once BD is suspected, adopted a multidisciplinary approach should be adopted (Table 2). There are no therapeutic guidelines for BD with cardiac involvement and a combination of anticoagulant, immunosuppressant and corticosteroid is the most accepted treatment. Anti-inflammatory agents act on the presumed inflammatory origin of this vascular complication, leading to a reduction of thrombus size (5, 7). The need for surgery is still discussed (8). In a study published in 2018, The European Alliance of Associations for Rheumatology (EULAR) suggested that the mortality rate is higher in patients undergoing surgery. The reason is that it triggers the vascular pathergy phenomenon that induces thrombosis. Thrombectomy is therefore reserved for life-threatening situations, as in our patient (4,7,8). The efficacy of vena cava ligation or vena cava filter placement in the preventing pulmonary embolism is also controversial (9). It should be considered for patients with a deep vein thrombosis or pulmonary embolism when anticoagulation therapy is not possible or fails (9). Our patient had a significant floating thrombus in the IVC very close to the renal veins and recurrent emboli despite appropriate anticoagulation. A vena cava filter could have compromised renal venous return, so the IVC was ligated without complications (as collaterals had already developed).

Because of the young age of our patient, we could have searched for a Mendelian genetic cause. Since 2016 a new entity of monogenic autoinflammatory diseases has been described. The tumour necrosis factor-α-induced protein 3 (TNFAIP3) gene mutation results in haploinsufficiency of a nuclear factor-κB regulatory protein A20 and patients develop mucosal and cutaneous symptoms resembling Behçet's disease in early childhood (10,11). Other frequent manifestations include recurrent fever and abdominal pain. However, vascular and cardiac symptoms appear to be rare in this entity (10).

Conclusions

In this report, we present a case of deep vein thrombosis and intracardiac thrombosis in the right heart ventricle, revealing Behçet's disease. This is an uncommon initial presentation of a rare disease in children. Only a high index of clinical suspicion and the exclusion of other potential causes allows a prompt diagnosis and optimal treatment. There are no therapeutic guidelines and several treatments have been used with varying outcomes. The patient was successfully

treated with anticoagulants, immunosuppressants, anti-inflammatory drugs and surgery. Surgical treatment should be reserved for life-threatening complications of Behçet's disease.

Conflict of interest

The authors have no conflict of interest to declare with regard to the subject discussed in this manuscript.

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