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THROMBOPHILIA: AN AMALGAM OF NEVER ENDING CLINICAL MANIFESTATIONS

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Abstract
Thrombophilia is a blood coagulation disorder, in which blood has an increased tendency to clot, with both arterial and venous localization, being responsible for multiple manifestations: secondary arterial hypertension, stroke, acute pancreatitis or intracardiac masses. We are presenting the case of a 21-year-old male patient, hypertensive, known with thrombophilia, who was sent for the echocardiographic evaluation of an intracardiac mass attached to the posterior leaflet of the mitral valve. The echocardiography and transesophageal echocardiogram showed a hyperechogenic, homogeneous intracardiac mass, attached to the posterior leaflet of the mitral valve, the clinical context and the echocardiographic appearance being suggestive for a thrombus. Given the context of thrombophilia and the hypertension's characteristics, we considered a secondary form of hypertension, the incriminated mechanism being represented by microthrombosis in the renal arterial circulation. There were two complications in the evolution of the patient: stroke and the recurrent acute pancreatitis, both being explained in the context of thrombophilia. The discharge echocardiography showed a favorable evolution, with a complete resolution of the thrombus under the anticoagulant treatment.
Keywords: *thrombophilia, intracardiac mass, arterial hypertension, stroke, pancreatitis.*

Rezumat
Trombofilia este o patologie congenitală sau dobândită, reprezentată de hipercoagulabilitate, în care sângele are o tendință crescută de formare a cheagurilor atât la nivel arterial, cât și venos, fiind responsabilă de multiple manifestări: hipertensiunea arterială esențială, accidentul vascular cerebral, pancreatita acută sau prezența formațiunilor intracardiace. Prezentăm cazul unui pacient în vârstă de 21 de ani, de sex masculin, hipertensiv, cunoscut cu trombofilie, ce a fost redirecționat pentru evaluarea ecocardiografică a unei imagini de adiție la nivelul valvei mitrale posterioare. Ecocardiografia transtoracică și transesofagiană au obiectivat o formațiune omogenă, hiperecogenă, atașată de valva mitrală posterioară, contextul clinic și aspectul ecocardiografic fiind sugestive pentru tromb intracardiac.



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Dată fiind prezența trombofiliei, cât și caracteristicile hipertensiunii arteriale, s-a pus problema unei hipertensiuni arteriale secundare, mecanismul incriminat fiind reprezentat de microtromboze la nivelul circulației arteriale renale. Evoluția pacientului a fost urmată de două complicații majore: accidentul vascular cerebral ischemic și pancreatita acută recurentă, ambele fiind explicate în contextul trombofiliei. Ecocardiografia la externare a obiectivat o evoluție favorabilă, cu rezoluția completă a trombului sub tratament anticoagulant adecvat.

Cuvinte cheie: *trombofilie, masă intracardiacă, hipertensiune arterială, accident vascular cerebral, pancreatită.*

Introduction

Thrombophilia is a blood coagulation disorder, in which blood has an increased tendency to clot, with both arterial and venous localization, being responsible for multiple manifestations: secondary arterial hypertension, stroke, acute pancreatitis or intracardiac masses[1-4]. Several cases of intracardiac thrombosis in patients with thrombophilia were published in the literature, some of them being recurrent after the anticoagulant treatment interruption. The most common genetic mutations are the deficiency of protein S, protein C, the presence of lupus anticoagulant, and factor V Leiden mutation [2]. Although the most common vascular diseases are venous thromboembolic events, cases of arterial thrombosis have been reported in the literature in patients with thrombophilia[5]. Renal thrombosis has been observed, especially in patients with lupus anticoagulant, which, in turn, may lead to the occurrence of a secondary form of hypertension[6,7]. The relationship between trombophilia and stroke is widely described, approximately 1-4% of strokes being diagnosed in patients with thrombophilia. However, in young patients, the incidence of thrombophilia reaches up to 40%, being responsible for most cryptogenic strokes[1,2,8]. Moreover, thrombophilia can induce gastrointestinal symptoms, the most common causes of acute pancreatitis by thrombotic or ischemic mechanism being reported in patients with lupus anticoagulant or anticardiolipin antibodies[9].

Case presentation

We are presenting the case of a 21-year-old male patient, who was sent for echocardiographic evaluation of an intracardiac mass attached to the posterior leaflet of the mitral valve. He was initially admitted for deficits of motor coordination of the lower and upper left limb. The patient had no significant family

history, was a smoker, denied alcohol consumption and had a chronic treatment with an anticoagulant and a venotropic, but was non-compliant with his treatment. However, he had a significant past medical history.

His health problems began at the age of 17, when he was diagnosed with thrombophilia with multiple mutations in the context of an episode of deep vein thrombosis:

- protein S deficiency
- factor V Leiden mutation
- factor XIII deficiency
- lupus anticoagulant
- anticardiolipin antibodies
- anti-beta2-glycoprotein 1 antibodies.

The evolution in the context of therapeutic non-compliance was followed in a relatively short time by a series of complications: chronic kidney disease stage G3, high values of blood pressure, with a systolic blood pressure up to 200mmHg and a relative resistance to treatment and a left occipital and right parietal stroke at the present time. As an associated pathology, the patient had recurrent acute pancreatitis, hemorrhagic gastroenteritis, duodenal ulcer and a venous ulcer of the left lower limb suprainfected with *Escherichia coli* and *Staphylococcus aureus*.

From the general physical examination, we noticed that the patient had a venous ulcer of the left lower limb, a blood pressure of 200/95mmHg, an epigastric pain, deficit of motor coordination of the left upper limb, normal cardiac and pulmonary auscultation.

Subsequent paraclinical examinations were conducted in three directions:

- the differential diagnosis of the intracardiac mass
- the etiological and functional assessment of arterial hypertension and its possible relationship with thrombophilia
- the associated digestive pathology and its possible relationship with thrombophilia.
- For the differential diagnosis of the intracardiac mass, transthoracic and transesophageal echocardiography were mandatory for a more accurate description, followed by biological parameters such as complete blood count, inflammatory markers and blood cultures.

The echocardiography showed a hyperechogenic, homogeneous intracardiac mass, with a size of 10/10 mm, attached to the posterior leaflet of the mitral valve and the presence of mild left ventricular hypertrophy with a normal kinetic (Figure nr. 1).

A more accurate characterization of the intracardiac mass was achieved by transesophageal echocardiogram, which highlighted the presence of a mass with a size of 11/6 mm above the posterior leaflet of the mitral valve, near the posterior mitral ring, with a minimum separation from the posterior mitral valve (see Figure 2).

The blood cultures were negative and the elevated C-reactive protein and presepsin values were interpreted in the context of venous ulcer of the left lower limb, suprainfected with *Escherichia coli* and *Staphylococcus aureus.*

The arterial hypertension was the second problem of our patient. Paraclinincal investigations were performed in order to established its etiology and its possible relationship with thrombophilia. The electrocardiogream (ECG) showed a sinus rhythm, with a heart rate of 70/minute and negative T waves in DII, DIII and aVF leads.

Given the context of thrombophilia and the patient's profile as well as the relatively sudden onset of hypertension, with elevated values up to 200/95mmHg and added



subsequent treatment resistance, a secondary etiology of the hypertension was taken into consideration.

Moreover, the impaired kidney function posed a problem of a renovascular cause, the incriminated mechanism being represented by the microthrombosis in the renal arteries, which required further investigations.

As the computed tomography angiography of the renal arteries could not be considered until the patient's stabilization, abdominal ultrasound was performed, showing renal asymmetry, with a small left kidney and old renal infarctions, which advocated for a renovascular etiology of hypertension by embolic mechanism, in the context of trombophilia. Also, several old splenic infarcts were detected, as well as infracentimetric gallstones and an inhomogeneous, hypoechogenic pancreas, which directed us to the last problem of our patient, respectively the associated digestive pathology.

Additionally, laboratory tests showed increased amylase and lipase values, in the context of his third episode of acute pancreatitis. Also, the high values of gamma-glutamyl transferase, alkaline phosphatase and lactate dehydrogenase were due to biliary distress, the patient also having gallstones. Given the fact that the patient denied alcohol consumption and that the pancreatitis was not related to overeating food addiction, the incriminated mechanism remained the ischemic-thrombotic one in the context of thrombophilia.

The final diagnosis were:

- Intracardiac thrombus attached to the posterior leaflet of the mitral valve
- Thrombophilia with multiple mutations
- Renovascular arterial hypertension
- Left occipital and right parietal ischemic stroke
- Chronic kidney disease stage G3b.

In the context of thrombophilia, other complications were associated, such as: splenic infarctions, renal infarctions, recurrent acute pancreatitis. Other associated comorbidities were: Left lower limb deep vein thrombosis complicated with chronic venous insufficiency Class 6 CEAP and lower left limb throphic venous ulcer suprainfected with *Escherichia coli* and *Staphylococcus aureus* and hemorrhagic gastroenteritis and duodenal ulcer.

The treatment was aimed in four directions:

1. the treatment of systemic thromboembolism in the context of thrombophilia
2. the treatment of arterial hypertension
3. the treatment of recurrent acute pancreatitis
4. the treatment of suprainfected venous ulcer.

For the systemic thromboembolism phenomena, the treatment with low molecular weight heparin was chosen during hospitalization. Due to the impaired kidney function, a beta-

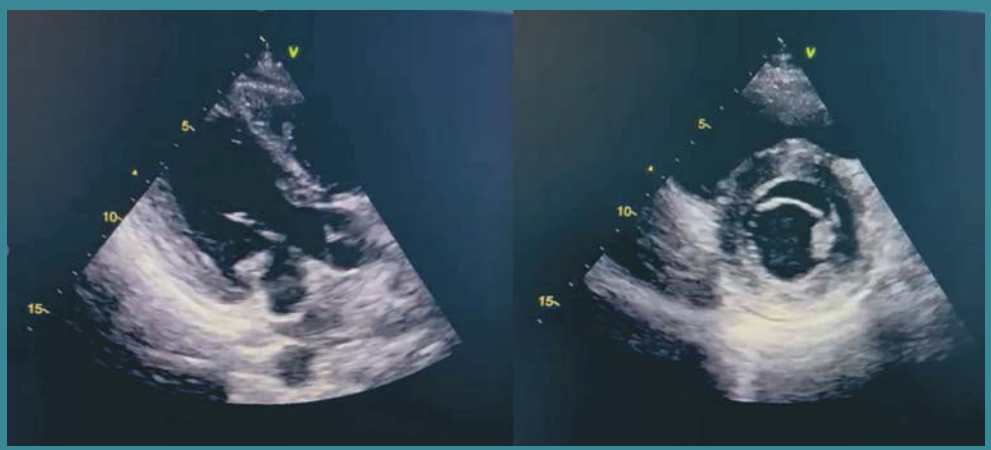


Figure nr. 1. *Transthoracic echocardiogram (parasternal long axis and short axis view) shows: a hyperechogenic, homogeneous intracardiac mass, attached to the posterior leaflet of the mitral valve*



Figure nr. 2. *Transesophageal echocardiogram: an intracardiac mass above the posterior leaflet of the mitral valve, near the posterior mitral ring, with a minimum separation from the posterior mitral valve*



Figure nr. 3. *Transthoracic echocardiogram: the complete resolution of the thrombus*



blocker, a dihydropyridine calcium channel blocker and an alpha-2/imidazoline receptor agonist were chosen for the treatment of resistant hypertension. Bowel rest was required for the treatment of the recurrent acute pancreatitis, which was associated with intravenous rehydration, an antispasmodic drug, an analgetic and a proton pump inhibitor. The suprainfected varicose ulcer was treated with amoxicilin and clavulanic acid, according to the antibiogram and local bandage.

The discharged echocardiography showed a favorable evolution, with a complete resolution of the thrombus under the anticoagulant treatment (Figure nr. 3). However, the neurological damage required recovery and the pancreatic disease supervision by a gastroenterologist.

The particularities of this case are represented by a young patient, known with thrombophilia, with multiple cerebral, renal and digestive thromboembolic events explained by an ischemic/thrombotic mechanism in the context of thrombophilia. In addition, also in the context of the basic pathology, the patient associated a rare location of the thrombus at the level of posterior leaflet of the mitral valve.

Discussions

In order to establish the etiology of the intracardiac mass attached to the posterior leaflet of the mitral differential diagnosis was made with infective endocarditis, a tumor or an intracardiac thrombus.

According to 2015 ESC Guidelines for the management of infective endocarditis, the diagnosis is made if either two major, one major and three minor or five minor of modified Duke's criteria are met[10]. However, apart from the echocardiographic aspect that suggests a possible vegetation, the patient did not present any major or minor criteria (negative blood cultures, without fever, without immunologic or vascular phenomena, without predisposing factors). We thus turn our attention to the echocardigraphic aspect, but the vegetation from the infective endocarditis is hypoechoic, attached to the valves in favorite places, with irregular surface and with its own mobility, exaggerated compared to the normal mobility of the valve. Therefore, according to the description from echocardiography and transesophageal echocardiogram, corroborated with clinical and paraclinical data, the diagnosis of infective endocarditis was unlikely.

Another differential diagnosis of the intracardiac mass was with a benign or malignant tumor, unlikely considering their very low incidence and their occurrence at an older age[4,11,12]. Moreover, they are more frequently located in the heart chambers, and from an echocardiographic point of view they are inhomogeneous, with an irregular contour.

The intracardiac thrombus remained within

the differential diagnosis of the intracardiac mass, the echocardiographic aspect and clinical context advocating for this diagnosis. In addition, an argument for the positive diagnosis of thrombus (and its differential diagnosis with other types of intracardiac masses) is its evolution, after a 4-week of an anticoagulation therapeutic test[11,12]. Therefore, considering the negative blood cultures, the clinical context and the ecocardiographic appearance, the image was not suggestive for vegetation or tumor, but rather for a thrombus.

One complication in the patient's evolution was the occurrence of stroke, the possible causes being explained by both the non-compliance with the drug treatment and the embolic source of the intracardiac thrombus attached to the posterior leaflet of the mitral valve. As we can find in the literature, the relationship between trombophilia and stroke is widely described, approximately 1-4% of strokes being associated with thrombophilia[2]. However, in young patients, the incidence of thrombophilia reaches up to 40%, being responsible for most of the cryptogenic strokes[13,14].

Another complication was the recurrent acute pancreatitis, the incriminated mechanism being the ischemic/thrombotic in the context of thrombophilia. The most common causes of acute pancreatitis by thrombotic or ischemic mechanism had been reported in patients with lupus anticoagulant or anticardiolipin antibodies, which provides an additional argument for this mechanism in our patient by the presence of these mutations[5,6].

Given the context of thrombophilia and the hypertension profile, as well as its relatively sudden onset, with elevated values up to 200/95mmHg, added subsequent treatment resistance, a secondary form of hypertension was considered.

Moreover, the impaired kidney function posed the problem of a renovascular cause, the incriminated mechanism being represented by the microthrombosis in the renal arteries. According to 2018 ESC/EHA Guidelines for the management of arterial hypertension, screening for secondary hypertension in patients with early onset hypertension (<30 years of age) in particular in the absence of hypertension risk factors (obesity, metabolic syndrome, familial history etc.), those with resistant hypertension, individuals with sudden deterioration in BP control, hypertensive urgency and emergency and those presenting with high probability of secondary hypertension based on strong clinical clues should be performed[15]. Renal thrombotic events have been observed, especially in patients with lupus anticoagulant, which was also identified in our patient.

Conclusions

In conclusion, there is a high probability of thrombophilia in young patients with deep vein thrombosis or stroke without any other risk factors. Moreover, for the differential diagnosis of an intracardiac mass the clinical context, the patient's profile and history and the laboratory parameters are important. Furthermore, in case of a patient with thrombophilia, the preferred anticoagulant for the long-term treatment is a vitamin K antagonist, as there are no studies to highlight the beneficial role of the novel oral anticoagulants. Lastly, in case of a therapeutic non-compliant patient, different locations of thrombi are being observed, especially in those with multiple mutations of thrombophilia.



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