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Recidiving Venous Thrombosis Revealing an Antiphospholipid Syndrome Associated with a Leiden Mutation of Factor V: A Case Report

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Abstract Recurrent thrombosis is a common complication in various pathologies and is part of the definition of antiphospholipid syndrome. We report an observation in which the patient presented with repeated thrombosis, due not only to an antiphospholipid syndrome with partial thromboplastin time with normal activator, but also to a resistance to active protein C linked to the existence of the Leiden factor mutation V. This observation confirms the most often multifactorial nature of thromboses and therefore encourages the search for resistance to activated protein C before an evocative clinic, especially if the routine coagulation assessment is normal.

Keywords: *leiden factor mutation V, thrombosis, antiphospholipid syndrome*

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1. Introduction

Various biological factors have been implicated in the occurrence of recurrent thromboses, such as presence of circulating anticoagulants, deficits in antithrombin or in proteins S and C. Resistance to the C-activated protein (RPCa), like B a mutation of the factor V gene (Leiden mutation), is also one of the etiologies to look for before any recurrent venous thrombotic process.

We report a case having presented repeated venous thromboses, within the framework of an antiphospholipid syndrome, associated with a RPCa and this despite a normal partial thromboplastin time with activator (TCA).

2. Observation

A 55 year old woman, having as a family history a systemic lupus erythematosus in the girl, diabetic on oral antidiabetic for 6 years, who presents in her personal history an appendectomy at the age of 28 years, cholecystectomy at the age of 34 years, a miscarriage, at the age of 38, complicated at 15 days from the post-abortion of a thrombosis of the left femoral vein, for which she benefited from anticoagulation with Warfarin for 3 months, with favorable evolution.

15 days after stopping warfarin, the patient presented with a recurrent thrombosis of the left femoral vein, for which the patient was put on warfarin.

The patient continued to have recurrences of right and left venous thrombosis, for which the patient was hospitalized in our establishment for specialized care.

On physical examination: conscious, stable, non-pyretic, in good general nutritional condition with a body mass index of 23 with blood pressure at 140/80 mmhg, heart rate at 60 beats per minute and respiratory rate at 30 cycles per minute .

Physical examination of the lower limbs showed a hot, edematous right lower limb, positive sign of Homans, and Doppler ultrasound confirmed the diagnosis

I / Biological examinations:

A / Hematological data:

1 / Hemostasis assessment:

- Prothrombin rate: 89%, Activated partial thromboplastin time: 35.70 seconds for a witness of 30.00.
- Protein C : 78%, protein S: 70%
- Antithrombin III: 100%
- DRVV Screen: 44.6 seconds with ratio of 1.4
- DRVV confirmed: 32.0 seconds with a ratio of 1.03
- The DRVV Screen report on DRVV confirms: 1.35

- The persistence of the circulating anticoagulant of lupus type beyond six weeks, made it possible to confirm a primary or secondary anti phospholipid syndrome. The family investigation led to the discovery of a girl with systemic lupus erythematosus.

2 / The speed of sedimentation:

- The sedimentation rate at 57 at the first hour

3 / Molecular biology:

The screening test for resistance to activated protein C is positive with a mutation of the factor V Leiden genes heterozygous.

4 / Blood count number:

- Hemoglobin at 12 g / dl, VGM at 79fl and CCMH at 33%;
- Inserts at 160,000 / mm3;
- Leukocytes 8360 / mm3

5 / Biochemical examinations:

- Fasting blood sugar: 6.66 mmol / l with an average blood sugar of 9.17mmol / l, glycated hemoglobin: 6.8%.
- Lipid and liver balance: normal.
- Proteinuria: 150mg / l, creatinuria: 7.2mmol / l with a proteinuria to creatinuria ratio of 21 mg / mmol.
- C-reactive protein at 28 mg / l.

Treatment with a direct oral anticoagulant (rivaroxaban) is instituted, with good clinical and biological progress.

3. Discussion

SAPL is characterized by venous and / or arterial thrombotic manifestations and / or miscarriages, associated with the long-lasting presence of autoantibodies, called anti-phospholipids (APL) [1,2]. To retain, the diagnosis, it is necessary to have a clinical criterion and a biological criterion of the criteria of the classification of Sapporo 1996 revised in 2006 summarized in table 1. In our observation, the diagnosis of SAPL is retained in front of arterial and deep vein thrombosis. associated with the presence of anti phospholipids at high levels. SAPL can be an apparently isolated entity (primary form) or more often associated with another autoimmune disease, in particular lupus [1]

Resistance B activated protein C (AAPR) is the most common risk factor for hereditary thrombosis [1,2,3,4]. Protein C is one of the main inhibitors of coagulation. Physiologically, it is activated by the action of the thrombin-thrombomodulin complex and will itself inactivate active factors V (Va) and active VIII (VIIIa) in the presence of protein S, calcium and phospholipids.

A mutation of the arginine codon for glutamine at 506 on the coagulation factor V gene causes an abnormality at one of the Va cleavage sites, the target of the action of activated protein C.

This mutated factor is called factor V Leiden. It has normal procoagulant activity but its inactivation is ten times slower than that of normal factor V. This causes a state of hypercoagulability. Screening is carried out first by the plasma phenotypic test. This evaluates the prolongation of the patient's coagulation time in the presence of purified C-activated protein (PCs). The test is made specific with respect to the Leiden mutation by the prior dilution of the plasma sample in a reactive plasma deficient in factor V. If the patient is affected, the ratio of clotting time with PCs to coagulation time without PCs is decreased [5]. The genetic origin of the abnormality is confirmed by studying the genotype by PCR B method from nucleated blood cells [6].

In the general Caucasian population, this anomaly is associated with de novo venous thrombosis in 20% of cases, recurrence in 65% of cases and familial thrombophlebitis in 30 to 50% of cases [7]. The frequency of the FV Leiden mutation is approximately 20-30% in subjects with a history of thrombosis, and it can reach 50% in selected thrombophilic patients [8,9]. The frequency of homozygous subjects has been evaluated at 0.02% [8,10,11]. They would have a risk factor of thrombosis multiplied by 80 compared to normal subjects.

Several studies have looked for a link between these two anomalies. In fact, Male et al. reported that the presence of anticoagulant lupus is significantly associated with acquired APR in lupus patients [13,14]. Some authors report that APLs can target activated protein C [7] and that the phospholipid-protein C complex can be recognized by APLs which are at the origin of acquired RPCA [14], others have suggested that 2GP1, an important cofactor of antiphospholipid antibody-cardiolipid antigens binding which instead has anticoagulant action present.

However, in the presence of phospholipids a procoagulant action by inhibiting the activity of activated protein C [7,14]. Furthermore, anticoagulant lupus can induce an RPCA phenotype in the absence of the factor V Leiden mutation [10]. However, it should be noted that patients with phenotypic RPCA have an increased risk of thrombosis even in the absence of the factor V Leiden mutation [12]. This amounts to saying that RPCA not induced by the presence of FV Leiden is an independent thrombotic factor [8].

The age of the first accident is variable, sometimes late. Most of the time, in the event of a heterozygous mutation, other risk factors are found: surgery, bed rest, pregnancy, oral contraceptives.

In addition, this observation shows that resistance to activated protein C must be systematically sought in the face of repeated thrombosis as an additional risk factor, even in the context of antiphospholipid syndrome with circulating anticoagulants, and that the latter must be sought despite a normal TCA in front of an evocative clinic.

The prevention of recurrence is the main problem for these high risk subjects. Our patient had a recurrence of thrombosis when stopping the K antivitamins.

However, after evaluation of the benefit-risk, prolonged use of a direct oral anticoagulant is recommended, such as rivaroxaban.

The therapeutic targets of direct oral anticoagulants (NOACs), such as rivaroxaban (anti-Xa), have a mechanism of action similar to that of LMWHs, being a drug with specific and direct action and with a low level of d drug interaction, it offers a promising future for patients poorly controlled by conventional anticoagulant therapy.

In addition, according to recent research, NOACs have been used in the treatment of antiphospholipid syndrome, generally with favorable results [16,17,18,19].

The series published by Malec et al. noted that 56 patients treated with rivaroxaban experienced a 5.8% recurrence of per year [17].

In studies by Haladyj and Olesinska on 23 patients and Son et al. out of 12 patients treated with rivaroxaban, 1 and 2 cases recurred, respectively [16,19].

Mention should also be made of the development of thrombotic events after the replacement of warfarin by a NOAC, as in the study published by Schaefer et al. with a series of 3 patients (one with dabigatran and 2 with rivaroxaban [20] and a case of catastrophic antiphospholipid syndrome after switching from warfarin to rivaroxaban [21]. Clinical trials are under development to determine the role of Direct oral anticoagulants in antiphospholipid syndrome [15,22].

4. Conclusion

Antiphospholipid syndrome is an entity characterized by thrombosis and / or obstetric complications with anti phospholipid antibodies. It can be primary or secondary. This often polymorphic entity must be known because it exposes a vital risk linked to thrombosis which may be greater in case of association with another anomaly of hemostasis.

A phenotypic resistance to activated protein C may be associated with SAPL in the absence of the factor V Leiden genetic mutation. The mechanism of this acquired resistance is not yet fully understood, but it should be noted that even phenotypic resistance in the absence of the genetic mutation constitutes an independent risk factor for thrombosis.

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