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Correspondence

First case with antithrombin deficiency, mesenteric vein thrombosis and pregnancy: Multidisciplinary diagnosis and successful management

1. Introduction

Mesenteric venous thrombosis (MVT) is a rare localization of thrombosis that is difficult to diagnose due to its non-specific clinical manifestations [1]. The main deleterious consequence of MVT is intestinal ischemia, which has a mortality of 20–50% [1]. Different prothrombotic states caused by heritable or acquired factors associated with MVT [1].

Antithrombin deficiency is the congenital risk factor most frequently associated with MVT [2]. However, as the levels of this key endogenous anticoagulant may be low in patients with acute thrombosis due to its fast consumption, deficiency of antithrombin in MVT may be difficult to be diagnosed by using functional methods. Accordingly, a correct identification of antithrombin deficiency in MVT should be performed by careful follow-up studies with serial antithrombin estimation, familial studies, or genetic tests.

Pregnancy is an acquired hypercoagulable state that is worsened with underlying thrombophilia [3]. Thrombosis during pregnancy mainly locates at lower limbs, and only 12 cases with MVT have been described in pregnant women.

We here present an exceptional case of a 7 week pregnant woman, with MVT and a new mutation in *SERPINC1* responsible for a type I antithrombin deficiency.

2. Case report

A 29 year old 7 week pregnant woman arrived to the emergency department with abdominal pain localized in the epigastrium, accompanied by diarrhea and vomiting. She reported no relevant medical history except for a family history of venous thromboembolism. Her father had suffered from unprovoked deep vein thrombosis of the lower extremities at the age of 49, and two paternal aunts developed early thrombotic episodes.

Blood tests revealed 19.800/uL leukocytes with neutrophilia, CRP 8.14 mg/dl; LDH 775 U/L; ALP 127 U/L; amylase 56 U/L. Abdominal ultrasound showed mesenteric vein, splenic and portal thrombosis. The fetus was alive.

Conservative management and anticoagulation with low molecular weight heparin (LMWH) was decided (Table 1). However, 24 h later, abdominal pain becomes more intense starting with rectorrhagia. Blood tests showed 36,700/uL leukocytes (88.4% N), CRP 13 mg/dl, lactate 11 mg/dl, LDH 452 U/L. New ultrasound showed significant dilation of the small bowel, free fluid and persistence of the thrombosis.

Laparoscopic surgical exploration was decided, revealing ischemia of 1 m of small intestine. Conversion to a midline laparotomy was performed with bowel resection. After surgery the patient went to the intensive care unit, where anticoagulation with sodium heparin was started (Table 1). The fetus was alive after surgery.

Due to the strong family history of thrombosis, thrombophilic tests (antithrombin, protein C, protein S, factor V Leiden, and prothrombin G20210) were done in the patient. Antithrombin tests were also done in her father, who was on long-term acenocumarol therapy. Only antithrombin tests (plasma anti-FXa activity evaluated by a chromogenic method) revealed positive findings. The proband and her father had antithrombin deficiency (28% and 47%, of values observed in reference plasma, respectively). Accordingly, antithrombin replacement therapy (Kybernin® P, CSL Behring) was started (Table 1). She also received anticoagulation with heparin, unfractionated heparin (UFH) first and low molecular weight heparin (LMWH) subsequently (Table 1).

Postoperative course was favorable. Two weeks after surgery a control ultrasound revealed that partial thrombosis persisted in the portal vein at the level of the hepatic hilum. The portal bifurcation and splenic vein were clean so the patient was discharged. The fetus was viable. Two months later a new ultrasound is performed showing no portal thrombosis.

Due to the difficulty to reach therapeutic anti-FXa levels despite antithrombin replacement and increasing LMWH dose, the patient was switched to acenocoumarol in the 13th week of pregnancy (Table 1).

In the 35 + 5 week the patient was admitted to hospital to prepare for delivery due to effacement of the cervix. She was converted to UFH and received antithrombin replacement therapy peripartum (Table 1). Postpartum was treated with increasing LMWH dose from prophylactic to therapeutic and bridged to acenocoumarol while on antithrombin replacement (Table 1).

A deep characterization of antithrombin deficiency was done in the proband and her father. Analysis of plasma antithrombin was only done in samples from the father since the proband had antithrombin replacement therapy. Electrophoretic analysis using denaturing (both under reducing and non-reducing conditions) and native (with and without 6 M urea) and latter immunodetection was performed essentially as described before [4]. These methods allow detection of quantitative defects but also are able to identify aberrant or minor forms of antithrombin as the latent conformation, polymers or disulfide-linked dimers. These studies support a type I deficiency with no detection of aberrant antithrombin in plasma (Fig. 1). Genetic analysis was performed in the proband. PCR and sequencing of the 7 exons and flanking regions of *SERPINC1*, the gene encoding antithrombin, was done with primers and conditions described elsewhere. This study revealed a heterozygous deletion of 31 base pairs which affects the final nucleotide of intron 6 and 30 bp of exon 7 (g.13913_1394del31pb; numbering according to the reference sequence: ENSG00000117601) (Fig. 1). The deletion eliminated the acceptor splicing signal and the first 30 nucleotides of exon 7 (Fig. 1). The deletion was confirmed by electrophoretic analysis of PCR products following the procedure described

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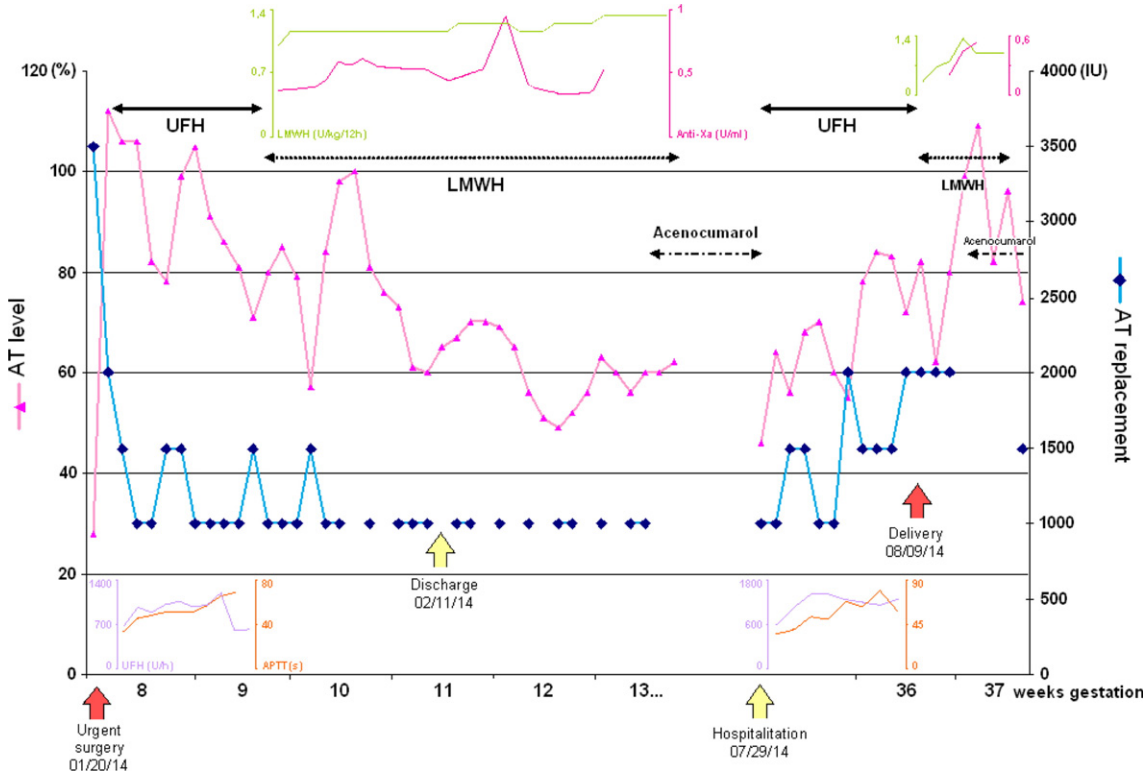
Table 1
Anticoagulation treatment during the evolution of the proband. Patient's weight: 60 kg and 70 kg in the 7 and 35 week of gestation respectively. Reagents used for plasma measurements on ACL TOP® IL Coagulation Systems: HemosIL®SynthASil (APTT), HemosIL® Liquid Antithrombin (AT levels) and HemosIL® Liquid heparin (anti-FXa levels). APTT control: 30 s. The LMWH used was enoxaparin.



before [5]. As shown in Fig. 1, the father also carried this deletion, which was also confirmed by sequencing.

After the diagnosis of antithrombin deficiency in the proband and her father, information from the parental family was requested in their origin country, Peru. Antithrombin deficiency was present in symptomatic relatives.

3. Discussion

Exceptional clinical cases are an excellent source of basic and clinical information that may help to the management of similar situations or conditions. We report our experience in the diagnosis and successful management of the first case of MVT of a 7 weeks pregnant women carrier of a type I antithrombin deficiency caused by a new mutation in *SERPINC1*.

Antithrombin deficiency is considered the cause of 1% of thrombosis in pregnancy [6]. Moreover, unusual localizations of thrombosis, particularly MVT, are relatively common among patients with antithrombin deficiency [2]. However, as far as we know, the combination of antithrombin deficiency, MVT and pregnancy has never been described and only two cases of MVT related to thrombophilia during pregnancy have been described in the literature. The first case involves a patient carrying the factor V Leiden polymorphism in heterozygous state who was handled conservatively with anticoagulation leading to success [7]. The second case was a patient with protein S deficiency who also required from surgical intervention with resection of a large segment of small intestine due to the mesenteric ischemia. Unfortunately, the patient died from sepsis [8].

The first goal in our case was a rapid diagnosis. The diagnosis of MVT in pregnant patients is difficult as some signs can be interpreted as normal changes of pregnancy. The family history of thrombosis, including a relative who also developed MVT during pregnancy, encouraged to address a potential MVT in our case. Ultrasound was crucial in identifying the etiology of abdominal pain as identified the MVT in our case.

Once the diagnosis of MVT is made, it is important to determine whether there is mesenteric ischemia. Management can be conservative with anticoagulation, control of the clinical course and repeated ultrasound scans under absence of ischemia [4]. The literature describes 3 cases of pregnant patients with MVT without mesenteric ischemia managed conservatively [7,9,10]. In all three cases, the pregnancy comes to term.

If there is a high suspicion of mesenteric ischemia and no firm diagnosis, laparoscopy will allow a direct visualization of the abdominal cavity, as a very reasonable diagnostic alternative in pregnant women. Ionizing radiation must be avoided and sometimes the problem can be solved with this type of approach. In our patient, given the poor outcome and high suspicion of intestinal ischemia, we chose laparoscopy for diagnosis.

Intestinal ischemia after venous thrombosis is uncommon in pregnant women. There are only 9 cases described: 2 after contraceptive intake, 2 had coagulopathies, 1 after caesarean, 1 due to toxic megacolon by CVM, 2 idiopathic and 1 due to hemoglobinopathy. In all of them except the caesarean and hemoglobinopathies, there was loss of the fetus and intestinal resection had to be performed. Delayed diagnosis of intestinal ischemia due to venous thrombosis may involve the death of the mother and fetus.