

Case Report

Acquired Antithrombin Type IIb Deficiency After Liver Transplantation: A Case Report

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A 3-year-old girl with multifocal hepatoblastoma was referred to our clinic for living-donor liver transplantation, the patient's father being the donor. Pretransplant evaluation revealed that the father presented partial asymptomatic antithrombin (AT) deficiency, with no inherited AT deficiency found in the girl. The genetic testing showed an AT type IIb deficiency responsible for a defect in the heparin-binding region of AT which is less thrombogenic but more common than the other AT qualitative defects. Her mother was ABO incompatible. Despite the thrombophilia on the father's side, transplantation was successfully performed under replacement therapy with intravenous AT concentrate and low-molecular-weight heparin thromboprophylaxis given to both the recipient and the donor. No thrombotic complications occurred. In the post-transplantation course, acquired partial AT deficiency was detected in the recipient, who received adjuvant chemotherapy without thrombotic complications. This case report highlights the relevance of full thrombophilic work-up before liver transplantation from a living donor, while illustrating that the procedure can be successfully performed in the case of AT deficiency on the donor's side provided that appropriate AT supplementation and thromboprophylaxis are administered to both the recipient and the donor.

Key words: Antithrombin-deficiency, hepatoblastoma, liver transplantation

Abbreviations: APCr, activated protein C resistance; AT, antithrombin; LMWH, low-molecular-weight-heparin; VTE, venous thromboembolism.

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Case Report

A 3-year old girl was referred to our center for liver transplantation, because of multifocal hepatoblastoma involving the left and right hepatic lobes, extending into the retrohepatic inferior vena cava (Grade IV hepatoblastoma; Ref. 1). As recommended by the SIOPEL protocol (1), the patient's liver disease was a definite indication for liver transplantation associated with pre- and postoperative chemotherapy (1–4). During the preoperative work-up, her father who was a candidate for living-donor liver transplantation was found to present partial antithrombin (AT) deficiency (AT levels estimated at 52% using a functional assay, with normal levels >80%), with no personal or family history of thromboembolic events. Genetic testing confirmed a g.2586C > T substitution (p.Pro41Leu) in exon 2 of the AT gene. This mutation which is responsible for a defect in the heparin-binding region of AT is more common but less thrombogenic than other types II qualitative deficiencies of AT (5). Unlike her ABO-compatible father, the child's mother was not considered a candidate for living-donor transplantation because of ABO incompatibility. No inherited AT deficiency was detected in the young girl. Despite the risk of AT deficiency transmission to the recipient and potential transplantation-induced thromboembolic complications for donor and recipient, our multidisciplinary team decided to carry out the procedure. To this end, AT replacement therapy and low-molecular-weight heparin (LMWH) thromboprophylaxis were initiated, under close clinical, biological and imaging monitoring.

Before the intervention, the father was administered a 2000 unit bolus injection of plasma-derived AT concentrate (AT, Baxter, 2000 U), which was repeated during the postoperative period to maintain AT concentrations at normal levels. In addition, subcutaneous LMWH thromboprophylaxis was initiated at a daily dose of 3800 anti-Xa units (Nadroparin, 0.4 cc/day), with the AT supplementation continued until the father's discharge on Day 8 and LMWH thromboprophylaxis until Day 18. Thrombotic complications were neither suspected clinically nor evidenced using serial abdominal ultrasounds. Seven days after the procedure, his AT levels were found unchanged, thus being unaffected by partial liver resection.

After total hepatectomy, the girl patient received a first AT bolus, followed by daily AT infusions (500–1500 units for a 16 kg body weight) to maintain AT basal levels above 80%

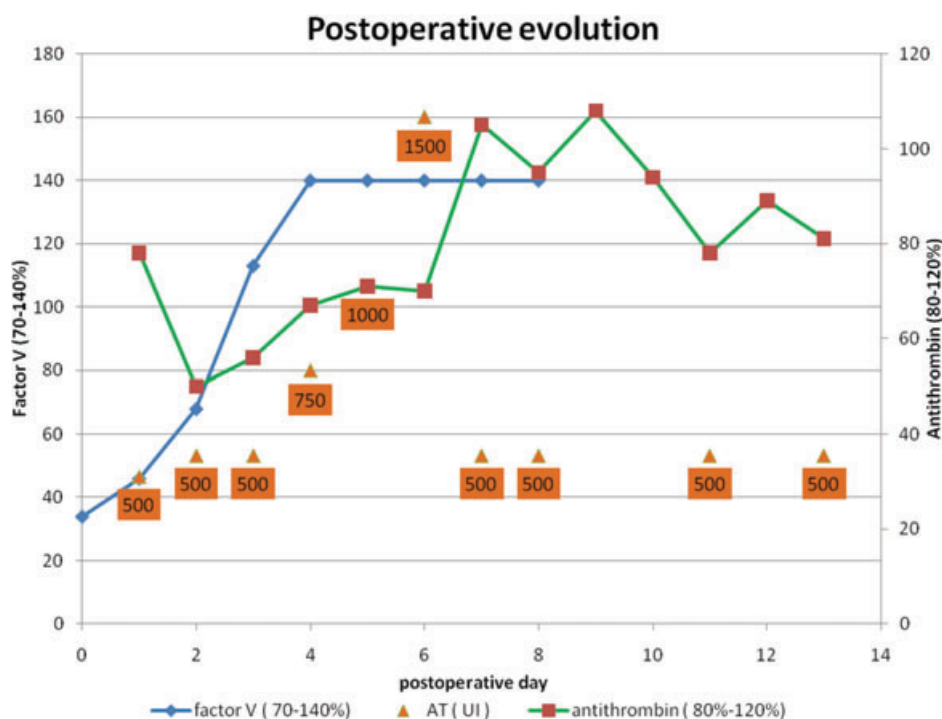


Figure 1: Replacement therapy with antithrombin (AT) concentrate and plasma AT and coagulation factor V levels in a liver recipient from a donor with AT deficiency.

(Figure 1), combined with LMWH thromboprophylaxis (750 IU Nadroparin, i.e. 50 IU/kg daily by continuous intravenous infusion). The immediate posttransplantation course was uneventful, as assessed by liver function tests and factor V levels Figure 1. During the first postoperative week, daily Doppler ultrasound revealed normal vascular permeability. Immunosuppressive treatment included basiliximab (Simulect[®], Novartis, Brussels, Belgium) at posttransplantation Days 1 and 4 and tacrolimus (Prograf[®], Astellas, Brussels, Belgium) for long-term immunosuppression therapy, with no liver rejection detected during follow-up. AT supplementation and LMWH prophylaxis were discontinued on Day 13, and the child was discharged with a standard postliver-transplantation treatment consisting of viral and *Pneumocystis carinii* prophylaxis (aciclovir 200 mg 2x/day and trimethoprim 6 mg/kg 3 days/week) in addition to tacrolimus (to achieve blood level of 8–10 ng/mL) as the sole immunosuppressive agent. After transplantation, the girl underwent adjuvant chemotherapy consisting of cisplatin and doxorubicin according to the SIOPEL protocol (1), with no further thromboprophylaxis given. No thrombotic complications occurred. As expected, AT levels measured 2 months after transplantation were low, notably at 49%. At 14 months posttransplantation, the child was alive and well with no evidence of malignant recurrence.

Discussion

The liver plays a central role in hemostasis and thrombosis by synthesizing procoagulation factors (coagulation factor I, II, V, VII and VIII, etc.) and coagulation inhibitors (protein

C, protein S and AT). Impaired liver production of factor VIII or IX leads to the clinical manifestations of hemophilia A or B, the two most common inherited bleeding disorders. By contrast, inherited thrombophilia is caused by deficiencies in coagulation inhibitors (protein C, protein S and AT) or more commonly, the consequence of point mutations in genes encoding for coagulant factor V (FV Leiden mutation) or factor II (G20201A prothrombin mutation). The most common form of inherited thrombophilia, factor V Leiden mutation, may be observed in up to 5% of subjects in certain populations. Contrarily, AT deficiency is very rare (<0.1–0.6%), as are protein C (0.2–0.3%) and protein S deficiencies (<0.1%; Ref. 6). Inherited AT deficiencies are either quantitative (type I) or qualitative (type II), as in our patient. Type II is subdivided into the more common, but less thrombogenic, type IIb deficiency caused by a defect in the heparin-binding region of AT and the less common, but more thrombophilic, type IIa variant caused by mutations in the thrombin-binding site. A pleiotropic type IIc deficiency also exists (5).

Owing to the liver's key function in synthesizing coagulation factors, liver transplantation likely impacts the hemostatic status of the recipient. In this context, it is well established that hemophilia in the recipient may be cured by liver transplantation (7), which according to published reports (8) is also the case for protein C deficiency. Furthermore, liver transplantation involving a donor with thrombophilia is likely to induce thrombophilia in the recipient. Conversely, liver transplantation may also correct thrombophilia in an affected patient. Given its high prevalence in the general population, factor V Leiden

mutation, which is responsible for activated protein C resistance (APCR), is the most common thrombophilia form studied in patients undergoing liver transplantation. Several published reports have dealt with the acquisition or correction of APCR abnormalities after liver transplantation (9–13), with thrombophilia shown to be a significant risk factor for thromboembolic complications during the perioperative period (14–16). Given this context, several authors have recommended that routine thrombophilia screening (screening for protein C, protein S, AT deficiency, APCR and prothrombin mutation) be conducted before liver transplantation so as to prevent the transmission of prothrombotic abnormalities from the donor to the recipient (17). Furthermore, thrombophilia patients have occasionally been excluded as living donor candidates in an effort to avoid donor thrombosis occurring during the perioperative period (18).

In our case, the urgency of the liver transplantation, owing to the risk of subsequent metastases, led us to recommend living-donor transplantation, despite orthotopic liver transplantation being considered the standard treatment for multifocal hepatoblastoma (1–4). Our decision was driven by the currently worsening shortage of appropriate postmortem liver donors within the Eurotransplant system. The living donor option was also privileged to graft a liver of high quality and size-matched and perform total hepatectomy and liver transplantation within a minimal time interval after the last chemotherapy.

During the preoperative work-up, asymptomatic AT deficiency was diagnosed in the girl's father, whereas her mother was shown to be ABO-incompatible. As alternative therapeutic option, liver transplantation could have been performed with the girl's mother being the donor, despite ABO incompatibility. However, in cases of ABO incompatibility, graft survival was found to be significantly impaired after transplantation because of a higher incidence of hyperacute rejection, vascular thrombosis and biliary injury (19,20). In addition, preoperative plasma exchanges may lead to enhanced immunosuppression, which likely aggravates the immune impairment induced by chemotherapy (19,20).

As regard the recipient, the potential long-term consequences of an acquired AT deficiency must be taken into consideration. Indeed, AT deficiency was reported to be linked to a high prevalence of venous thromboembolism (VTE), ranging from 6% to 66% depending on the study, the prevalence being somewhat lower in patients with AT type IIb deficiency (around 6%; Ref. 5), as was the case in our patient. It should be pointed out that the results of the mutation analysis were not available at time of transplantation and did not influence our therapeutic attitude. In these patients, the risk of VTE events seems to be low during childhood, significantly increasing around the age of 20. Oral contraception is contraindicated in AT-deficient patients, and pregnancy puts them at a particular high-

risk of VTE events. In the absence of efficient thromboprophylaxis, 31–41% of AT deficient women develop VTE events during pregnancy, with the rate of fetal loss being significantly increased in AT deficient carriers (5). Therefore, heparin thromboprophylaxis is highly indicated in the event of transient risk situations such as surgery, immobility and pregnancy. As some of these patients are likely to present heparin resistance, administration of higher heparin doses is required to obtain a therapeutic effect. Given this context, replacement AT therapy should be envisaged, especially in the case of surgery (21).

AT deficiency is an autosomal genetic disorder, with over 130 reported mutations involving the AT gene. Our patient had an acquired form of the AT deficiency phenotype, without carrying any AT gene mutation, resulting in a phenotype-genotype discrepancy. The only means of diagnosing posttransplantation AT deficiency is the measurement of AT levels. Of note is that the girl's AT deficiency will not be transmitted to her descendants.

Thrombophilia screening before liver transplantation is aimed to minimize the risk of perioperative thrombosis in both the donor and the recipient. Although there is a limited experience regarding the risk of thrombosis in patient with type IIb AT deficiency undergoing liver transplantation, we considered that the persistent AT deficiency in our patient could have precipitated thrombotic complications possibly of the hepatic artery or the portal vein during the restoration of a normal liver synthesis. The recommended treatment was therefore the combined administration of LMWH and AT concentrates (21,22), with the objective to maintain AT levels above 80%. To avoid multiple subcutaneous injections, LMWH was given peroperatively via intravenous continuous infusion (23,24).

Conclusion

To the best of our knowledge, this is the first report of a living-donor liver transplantation involving a donor with AT type IIb deficiency caused by a defect in the heparin-binding region and less thrombogenic than other AT deficiencies. This kind of transplantation has been reported in cases of donors or recipients with more common inherited forms of thrombophilia, such as factor V-Leiden mutation and inherited protein C deficiency. Our report suggests that a full thrombophilia work-up, including AT dosage and characterization, should be considered before liver transplantation to reduce the risk of thrombosis during the perioperative period. In our case, thrombosis prevention was successfully managed in both the donor and the recipient by means of AT concentrate administration and LMWH thromboprophylaxis, as no thrombotic complications occurred during follow-up. In our opinion, AT deficiency should not be considered as a definite contraindication to liver transplantation provided that appropriate measures are taken during the perioperative period.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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