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CASE REPORT

Protein S deficiency in a living liver donor

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Summary

Protein S deficiency is a thrombophilia associated with increased risk of thromboembolic episodes in affected patients. Traditionally, protein S deficiency in a potential donor was considered an absolute contraindication to living donor liver transplantation, both due to the increased risk incurred by the thrombophilic donor as well as the risk of transmitting the thrombophilia to the liver recipient, as protein S is predominantly produced by the liver. We present the first successful case of living donor liver transplantation using a donor with asymptomatic protein S deficiency. Interestingly, whereas the donor continued to have protein S levels approximately 50% of normal, the recipient maintained normal levels of protein S post-transplant, potentially due to compensation by extra-hepatic protein S production. We discuss the prior literature of protein S deficiency acquired via liver transplantation, and we evaluate potential criteria by which the safety of transplants utilizing this pool of donors may be enhanced.

Introduction

Protein S deficiency is an autosomal-dominant thrombophilia linked to an elevated risk of venous thromboembolic events (VTEs). Although protein S deficiency is uncommon in the general population (with a prevalence ranging from <0.2% in Western Europe [1] up to 1.12% in Japan [2]), afflicted patients suffer from a relative risk of thrombosis or pulmonary embolism that is 5–10 times higher than their relatives with normal protein S function [3–5]. Indeed, estimates from several case series conclude that 2.4–3.8% of patients with spontaneous VTE have deficient protein S activity [6,7]. As protein S is predominantly (although not exclusively) produced in the liver, protein S deficiency in a donor has traditionally been an absolute contraindication for liver transplantation [8,9]. Indeed, symptomatic acquired protein S deficiency resulting from liver transplantation utilizing a graft obtained from a deceased donor has been described [10].

Here, we report the first successful case of a living donor liver transplant utilizing a donor with protein S deficiency. In contrast to earlier reports, the transplant recipient maintained normal protein S levels post-transplant, suggesting that extrahepatic protein S production in some recipients can compensate for liver grafts producing low levels of protein S.

Case report

A 27-year-old woman underwent medical evaluation for living donor liver donation to her mother, a 60-year-old woman with autoimmune hepatitis who had recently developed encephalopathy, oesophageal varices and ascites. Despite the severity of her symptoms, her MELD score was only 20–22. Given her blood type (type A) and the fact that she was listed in a region where the average MELD at transplant is 28, the prospect of a prolonged wait for a deceased donor organ prompted consideration of a living donor liver transplant.

At the time of initial evaluation, the donor had no significant past medical history, including no previous history of thromboembolic events. Her pre-transplant laboratory work-up was unremarkable, except for a protein S functional activity of 41% (reference: 70–140%) and free protein S antigen level of 52% (reference: 70–140%). These were attributed to an acquired deficiency due to oral contraceptive use, but a month after discontinuation, her protein S functional activity and free antigen level remained depressed (44% and 53% respectively). However, given her lack of personal or family history of thrombophilia and the relatively mild depression of protein S levels, our haematology consultants thought it exceedingly unlikely that she had true protein S deficiency, and they attributed her low levels to delayed recovery after cessation of contraceptives.

At this point, the donor's mother began to clinically deteriorate, developing a new oxygen requirement that was concerning for hepatopulmonary syndrome. Despite this, her MELD scores remained relatively low. Based on the opinion of our haematology consultants that (i) the potential donor had no intrinsic protein S deficiency and (ii) the temporary increased risk of thromboembolic complications due to transient reduction in protein S levels could be safely managed with fresh frozen plasma (FFP) infusion, a decision was made to proceed with living donor liver transplantation.

The donor underwent an uneventful right hepatectomy, and the resulting graft was transplanted into the recipient, which continues to have excellent function. At the last clinic visit, a year post-transplant, the recipient showed no evidence of protein S deficiency, with a protein S functional activity of 111% (Table 1). Peri-operatively, the donor received standard post-operative VTE prophylaxis and four units of FFP daily for the first five post-operative days. However, 2 years after donor hepatectomy, her protein S functional activity and free antigen level were still 54% and 55%, respectively, despite never resuming oral contraceptive use, findings consistent with a genetic protein S deficiency that was unappreciated at the time of transplant. In accordance with current clinical guidelines, sequencing of her *PROS1* gene was not pursued due to its clinical unreliability in diagnosing protein S deficiency, as mutations in the *PROS1* gene are not detected in approximately 50% of patients with protein S deficiency due to the failure of standard screening methods to detect common large deletions and insertions in the *PROS1* gene, as well as interference from a protein S pseudogene [11]. A factor VII level was obtained to exclude vitamin K deficiency or impaired hepatic synthetic function from her hepatectomy, but this was normal at 82% (reference: 60–140%). Given the combination of her lack of thromboembolism history and protein S levels >40%, her physicians recommended that she not receive prophylactic anticoagulation when she later decided to conceive, and she subsequently underwent an uneventful pregnancy, delivery and recovery.

Discussion

Living donor liver transplantation was intended to expand the supply of available organs, but stringent donation criteria have potentially excluded some viable donors. Traditionally, patients with coagulopathies or thrombophilias have been disqualified as liver donors, due to the risk to the donor from their underlying condition and the risk of transmitting these blood disorders to the transplant recipient, as most clotting factors and thromboregulatory proteins are predominantly produced in the liver [8,9]. Indeed, donor-to-recipient transmission of factor VII [12], factor XI [13], factor XII [14], protein C [15] and protein S deficiency [10] have been reported.

Here, we describe a successful living donor liver transplant from a donor with protein S deficiency. Interestingly, the recipient failed to develop protein S deficiency after receiving this protein S deficient liver graft, maintaining normal protein S functional activity even a year post-transplant. To explain this finding, we hypothesize

Table 1. Coagulation study values of liver transplant donor and recipient.

Coagulation study (normal range)	Donor initial pre-transplant evaluation	Donor, 1 month after oral contraceptive discontinuation	Donor, Post-transplant day #2	Donor, 2 years post-transplant	Recipient, Pre-transplant	Recipient, 1 year post-transplant
Protein S functional activity (70–140%)	41	44	31	54	91	111
Free protein S antigen level (70–140%)	52	53	51	55	–	–
Prothrombin time (10.3–13.2 s)	12.8	12.8	19.1	13.1	15	12.4
aPTT (22.1–34 s)	31.1	29.7	48.5	37.3	52.5	28.9
INR	1.1	1.1	1.8	1.1	1.4	1.0
Fibrinogen (150–400 mg/dl)	271	246	323	299	–	–
Factor VIII (50–200%)	152	151	117	138	–	–

that the extrahepatic protein S production of the recipient was able to compensate for the aberrant protein S production by the liver graft. It is well established that in addition to the liver, protein S is produced by a variety of other cell types such as endothelial cells, megakaryocytes, osteoblasts, Leydig cells and vascular smooth muscle cells [16,17].

This report stands in contrast to an earlier report of protein S deficiency transmitted via a liver transplant from a deceased donor [10]. The differing clinical outcomes between these two cases can probably be attributed to the clinical heterogeneity of protein S deficiency. Indeed, over 200 unique mutations in the *PROS1* gene encoding protein S have now been described [18], resulting in a spectrum of disease ranging from 'intermediate' variants with serum protein S level that are approximately 30–70% of normal to 'severe' variants associated with virtually no protein S production [19]. Unsurprisingly, these severe disease mutations have a heightened risk of thromboembolic complications compared with 'intermediate' gene variants [4,19].

Importantly, the donor described in this current report appears to have an intermediate phenotype of protein S deficiency, as she remains asymptomatic with no history of VTE and is capable of maintaining approximately 50% of the normal level of free protein S. The most likely explanation for the transmission of protein S deficiency described earlier by Schuetze and colleagues [10] is that the donor employed in their case report had a more severe deficiency in protein S levels compared with the donor in the current report, producing such a low level of protein S that it could not be compensated for by the recipient's extrahepatic protein S production. What can be considered a 'safe' level of residual protein S production to consider liver donation by a patient with protein S deficiency? Although conclusive evidence is lacking, recent epidemiological studies performed in families with protein S deficiency may serve as a guide. These studies found that an incremental risk of VTE was only incurred by patients with free protein S levels less than 30–40% of normal controls [20,21]. The donor in this current report maintained protein S levels considerably above this threshold, perhaps explaining why neither she nor the recipient developed any complications from the transplant.

Although we would not have performed this transplant had the donor's genetic protein S deficiency been recognized earlier, the unexpected preservation of normal protein S levels in our recipient offers the possibility that patients with 'intermediate' protein S deficiency (as indicated by an asymptomatic history and protein S levels >40% of normal) could potentially serve as living donors for liver transplantation with acceptable risk to donor and recipient. If this 'safe' subset of protein S deficient donors is confirmed, it would have important clinical implications in expanding the eligibility criteria for living donor transplants, particularly in Japan where there is a high prevalence of protein S deficiency and a reliance upon living donors [2]. Undoubtedly, though, donors with protein S deficiency must be approached with extreme caution and comprehensive informed consent. Utilization of grafts from these donors will require an individualized assessment of the risks and benefits offered to potential transplant recipients, similar to the assessment used for recipients of other marginal grafts (e.g. split-liver grafts or grafts obtained from extended criteria donors). Further work will be required to validate these conclusions regarding the potential safety of transplants using this unique donor population.

Authorship

WK, HY, EV, NE, TK, JM and MH: contributed to the clinical care of the patients. WK, HY and MH: wrote the manuscript.

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