Orthotopic Liver Transplantation in a Patient with Severe Haemophilia A and High Titre Factor VIII Inhibitor

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Introduction

Orthotopic Liver Transplantation (OLT) can successfully treat hepatitis C-associated liver cirrhosis. We describe the peri-operative haemostatic management and post-operative complications in an 48 year old Caucasian with severe HA and high titre FVIII inhibitor levels at the time of surgery.

To date, the literature describing OLT in patients with haemophilia A (HA) and high titre FVIII inhibitors present at the time of surgery is limited. The most closely comparable published case is that of Khakhar *et al* [1]. OLT in this patient with a high-titre FVIII inhibitor resulted in catastrophic microangiopathy, haemorrhage and death in the early post operative period.

Long term survival after OLT in patients with HA and FVIII inhibitors has solely been described in patients with low titre FVIII inhibitors (titre of 1.2 BU) or in patients successfully established on an immune tolerance regimen (FVIII inhibitor titre of <2 BU at the time of surgery) [2, 3 & 4].

Case Summary

The development of an FVIII inhibitor was first documented in our patient during childhood following on demand treatment with plasma derived factor VIII concentrate. Immune tolerance therapy was not attempted.

Exposure to non-virally inactivated plasma derived FVIII concentrate prior to inhibitor development led to infection with Hepatitis C genotype 3. The patient was seronegative for the HIV and Hepatitis B viruses.

Routine Fibroscan monitoring in 2010 identified evidence of liver cirrhosis. Subsequently the patient developed progressive hepatic decompensation and portal hypertension with variceal bleeding. Following lengthy consideration of the operative risk the patient was listed for OLT.

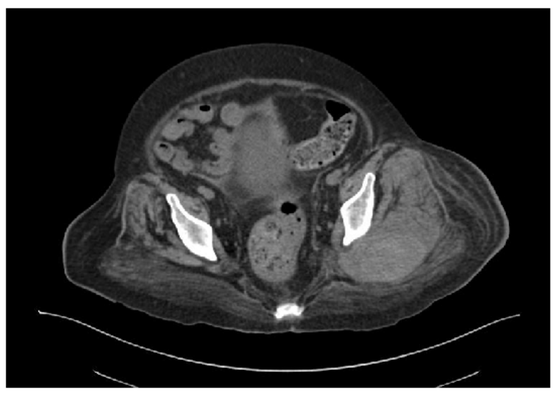
Haemostatic Management and Results

OLT was undertaken in July 2011. 100 $UKg^{-1}$of FEIBA™ was administered to the patient immediately prior to commencing the procedure. During the anhepatic phase 1g of Tranexamic acid was given. NovoSeven® 90μgKg^{-1} was administered twice during the OLT procedure to control excessive bleeding.

Blood product transfusion was undertaken in accordance with standard departmental guidelines based upon thrombelastography (TEG). Intra-operative transfusion requirements were: 15 units of packed red cells, 20 units of FFP, 1 unit of Platelets.

Intra-opertaive blood loss was recorded as 6400ml with a further 350 ml being lost during the subsequent two postoperative days.

Twice daily FEIBA™ 100 UKg^{-1} was administered during the first 48 hours postoperatively. From 72 hours the dosage of FEIBA™ was reduced to 80 UKg^{-1} twice daily with further reduction at 144 hours to 60 UKg^{-1}. From day twelve 60 UKg^{-1} FEIBA™ was administered once daily until day 20.



On-demand FEIBA™ was used during the patient's rehabilitation & physiotherapy. Notably, on the 68th day post procedure the patient received 100 $UKg^{-1}$of FEIBA™ for a large left gluteal haematoma

FVIII inhibitor titre

The Pre-operative FVIII inhibitor titre was measured at 58 BU/ml. During the immediate postoperative phase the FVIII inhibitor titre fell to a nadir of 0.8 BU. This was possibly due to the dilutional effect of large volume transfusion in the intra-operative period. A concurrent increase in FVIII levels was simultaneously observed due to FVIII production by the transplanted liver. A subsequent anamnestic response to FVIII was witnessed with inhibitor levels peaking at 2355 BU on day 15. This response occurred despite the use of an immunosuppressive regimen including Mycophenolate mofetil, Prednisolone and Tacrolimus given to prevent graft rejection.

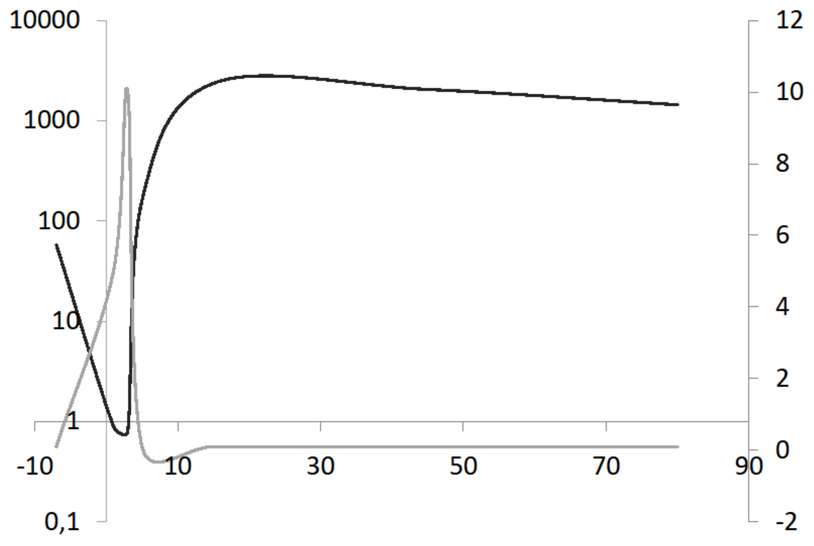
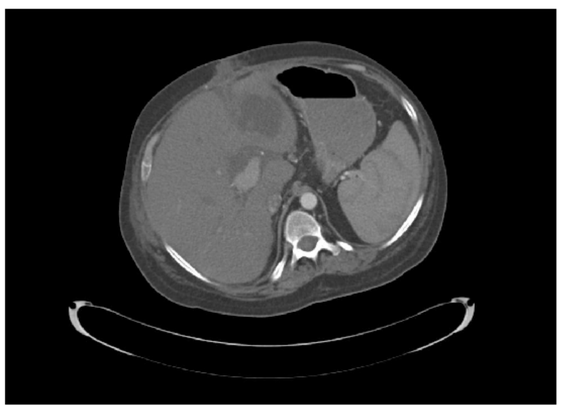


Figure
Plot demonstrating post operative days on the X axis against FVIII inhibitor titre (BU) on the left Y axis and plasma FVIII levels (IU/dL) on the right Y axis.

Late Complications

At day 90 computerised tomography undertaken to investigate a fever demonstrated hepatic artery thrombosis (HAT) with secondary liver abscess formation. The liver abscess was drained percutaneously following administration of 100 $UKg^{-1}$of FEIBA™. A single further dose of 75 UKg^{-1} was given 12 hours later.



Effective management of HAT mandates re-transplantation. Unfortunately the patient was unsuitable for this procedure. Following a further 105 days the patient died due to sepsis and liver failure as a consequence of HAT.

Discussion and Contribution to Practice

Whilst we believe this to be the first description of successful OLT in a HA patient with a high titre FVIII inhibitor present at the time of surgery, the late complication of HAT was catastrophic. Important practice points include:

1. The presence high titre FVIII inhibitors does not preclude successful haemostatic management OLT surgery
2. Massive transfusion may provide a temporary reprieve from FVIII inhibitor function
3. The immunosuppressive regimen used for transplant rejection did not prevent anamnesis of the FVIII inhibitor. Nor was the FVIII production of the grafted liver sufficient to neutralise the FVIII inhibitor
4. On-demand FEIBA therapy may have contributed to the development of HAT. This is an important consideration for clinicians managing such patients as the consequences are devastating.

References

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