Rare disease

Heparin-induced thrombocytopenia associated with acute liver graft failure

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Summary

An orthotopic liver transplantation (OLT) is of a proven benefit in an acute liver failure (ALF). Heparin-induced thrombocytopenia (HIT) is strongly associated with thromboembolic complications. We present the case of a 56-year-old patient who underwent an OLT owing to an ALF of unknown aetiology. HIT type II with consecutive hepatic and portal vein thrombosis caused progressive graft failure. Total hepatectomy and porto-caval shunt were performed to reduce the toxic effects of liver cell necrosis such as multiorgan failure involving the respiratory, renal and cardiovascular systems. A suitable liver graft was allocated after an anhepatic bridging period of 56 h. Specific complications due to end-stage liver failure—such as acidosis, coagulopathy, decrease of vascular resistance, cerebral oedema, myocardial infarction and right heart failure—were treated. Following a re-OLT, the patient made a complete recovery. We present a rare case of HIT-associated early liver graft failure followed by a prolonged anhepatic phase and finally a successful re-OLT.

BACKGROUND

An acute liver failure (ALF) is associated with high morbidity and mortality. An orthotopic liver transplantation (OLT) is of proven benefit in ALF and cures approximately 90% of the patients with terminal or preterminal liver failure.¹ The most frequent complications in the perioperative and postoperative periods are caused by haemostatic or immunological disorders, haemodynamic disturbances, cardiac dysfunction, infections, renal failure, primary graft dysfunction or acute rejection.

Early progressive liver graft failure generally causes fatal multiorgan failure due to the toxic effects of liver cell necrosis involving the respiratory, renal, cardiovascular and cerebral systems.^{2–5} Re-OLT is the only therapeutic option. But the nature of organ donation is very uncertain and a new donor liver is often not allocated in time. However, the time frame for transplantation is strictly limited because patients would die rapidly due to the toxic effects of progressive cell death. Thus, a two-stage procedure has been widely advocated.^{2–4} The first stage is a relaparotomy with a total hepatectomy of the necrotic graft with a temporary portacaval shunt. Subsequently, a bridging period under anatomic anhepatic conditions must be performed until the allocation of a new graft. After a successful allocation OLT can be performed in the second stage. The bridging therapy in the intensive care unit (ICU) is focused on preserving vital organ functions or on assisting organ functions with corresponding devices (eg, mechanical ventilation, renal replacement therapy (RRT), artificial liver support systems, figure 1) with the aim of prolonging the time window for transplantation and to optimise the preoperative condition of the patient. But the absence of vital hepatic functions such as detoxification, metabolism and protein synthesis cannot be compensated for a long time.

Heparin-induced thrombocytopenia (HIT) is an adverse immune-mediated reaction in which antibodies are generated usually towards complexes of soluble platelet-factor 4 (PF4) and heparin. HIT affects 1–5% of treated patients⁵ and is strongly associated with thromboembolic complications.

There is no evidence that patients undergoing an OLT have a greater risk of developing HIT.⁶ But the prevalence of PF4 antibodies might be greater because in this cohort, patients are more likely to be pre-exposed to heparin before transplantation. HIT-associated acute liver graft failure after an OLT is very rare and has previously been reported only in a single case report.⁷

CASE PRESENTATION

A 56-year-old man (weight 90 kg; height 180 cm and body mass index (BMI) 28) was hospitalised with symptoms of acute hepatitis (jaundice, elevated liver enzymes, fatigue). His condition rapidly worsened within 48 h into ALF with coagulopathy, progressive encephalopathy and hepatorenal syndrome with an MELD score of 35. Thus, he was listed as a 'high-urgency' candidate for an OLT. There was no evidence of severe thrombocytopenia before an OLT (preoperative platelet count (PLT) 136 000/mm³). The patient received no preoperative anticoagulation because of a severe hepatic coagulopathy with a spontaneous international randomised ratio (INR) of 2.8.

A full-size (1600 g) postmortem-donated ABO compatible liver was transplanted within the next 36 h. The donor was a 58-year-old woman (weight 65 kg; height 165 cm and BMI 24) who died due to cerebral aneurysm bleeding. The levels of aspartate/alanine aminotransferases (AST/ALT) were 42 and 46 U/l, respectively. The bilirubin level was 6.8 µmol/l; the sodium level was 145 mmol/l.

Figure 1 Mechanical assistance of vital organ function is an integral component of the anhepatic bridging therapy in the intensive care unit: mechanical ventilation (green arrow), renal replacement therapy (RRT) with high-volume continuous veno-venous haemofiltration (CVVH, white arrow) and artificial liver support systems (MARS, red arrow). Haemodynamic assessment to guide vasopressor dosages, inotropic agents and volume therapy was enabled by transcardiopulmonary thermodilution (blue arrow).

and the INR being 1.3 at the time of donation. The cold ischaemic time (CIT) was 790 min and the warm ischaemic time (WIT) was 65 min. The liver was implanted in the modified piggyback technique with a side-to-side cavo-caval anastomosis without veno-venous bypass. Intraoperative severe right heart dysfunction with consecutive liver venous congestion led to subcapsular haemorrhage, necessitating liver packing for 48 h. Six hours after an OLT, low-dose unfractionated heparin (UFH) (10 units/kg/h) was continuously administered intravenously. The initial postoperative clinical course on the ICU was uneventful and graft function was good. A Doppler ultrasound demonstrated adequate graft perfusion, as was already shown intraoperatively on routine postreperfusion and postfascia closing Doppler ultrasound. Immunosuppression was started with tacrolimus and prednisolone. The patient's renal function was still impaired and he needed RRT until the third postoperative day (POD). Postoperative PLT showed normal values (above 100 000/mm³) up to the second POD followed by a non-specific moderate thrombocytopenia (PLT ranging from 50 000 to 90 000/mm³). This trend was not unexpected because thrombocytopenia after an OLT is a well-recognised and common early postoperative phenomenon with a vague aetiology (eg, intraoperative platelet activation, platelet consumption in the early posttransplant period, inadequate thrombopoietin, 'hypersplenism' or drug-induced myelotoxicity). On the fifth POD, the patient was discharged from the ICU in a good condition and anticoagulation was switched to prophylactic low-molecular-weight heparin (Enoxaparin) on the sixth POD. At the eighth POD, the PLT fell below 20 000/mm³. In the absence of any clinically important haemorrhage, it was decided that the thrombocytopenia should remain untreated.

However, at noon of the 11th POD the patient was readmitted to the ICU because of encephalopathy, agitation, hyperventilation and massive lactate acidosis (figure 2, serum lactate level 9.0 mmol/l, pH 6.94, pCO₂ 18 mm Hg, base excess 24.0). Transaminases (AST 1331 U/l and ALT 639 U/l) were increased and liver synthesis was impaired (INR 1.85, factor V activity 28.1%). Soon after admission to the ICU, the patient's systemic vascular resistance decreased and he needed vasopressors to have a stable arterial blood pressure (figure 2). Owing to progressive respiratory failure and loss of consciousness, the patient required endotracheal intubation and mechanical ventilation.

At the time of readmission to the ICU, PLT demonstrated severe thrombocytopenia (19 000/mm³). Most recently erythematous skin lesions were observed at the subcutaneous puncture site of the Enoxaparin injections. Because of these findings, HIT II was tested. However, the diagnosis of HIT type II was carried out on the 11th POD based on a high pretest clinical probability (seven of eight points according to the four Ts scoring system) and positive findings in both the heparin/PF4 immunoassay (HPIA) and the heparin-induced platelet activation assay (HIPA) which is an established functional HIT assay used in most European countries. While the HPIA revealed only weak reactivity, the HIPA showed the typical HIT pattern, clearly establishing the clinicopathological diagnosis of HIT type II.⁸ Anticoagulation therapy was immediately switched to anti-Xa controlled danaparoid sodium (2.0 units/kg/h). At this point, no thromboembolic complications were evident.

Progressive graft failure with consecutive severe multiorgan dysfunction occurred due to the systemic response to excessive liver cell necrosis. Doppler ultrasound now showed echogenic-organised thrombotic material in the

Figure 2 Clinical course after the first OLT: progressive graft failure on the postoperative day 11 exhibited increased serum lactate levels and demand of vasopressors noradrenalin (red dot) and vasopressin 0.02 Units/min. Improvement of lactataemia (green), haemodynamics and clinical status due to renal replacement therapy, hepatectomy and artificial liver supporting system (MARS); secondary excessive increase in lactate and vasopressors during the prolonged anhepatic conditions.

main portal vein with the remaining partial flow but increased mean velocity. On the day of ICU-readmission (11th POD), urgent relaparotomy was performed unmasking extensive thrombosis of the hepatic and portal veins (figure 3). Given this situation, the decision was made to treat the patient with a two-stage procedure. Total allograft hepatectomy and temporary porto-caval shunt were completed during this laparotomy to counteract the soaring lactate acidosis and extensive demand of vasopressors (figure 2). There was no sign of stenosis or stricture of the venous, portal-venous or arterial anastomosis, respectively. The patient was immediately listed for 'highly urgent' re-OLT.

To support the anhepatic bridging period bicarbonate-based high-volume continuous haemofiltration (CVVH) was initiated on the ICU directly after allograft hepatectomy to eliminate serum lactate (figure 1). Furthermore extracorporeal albumin dialysis (MARS, Gambro, Rostock, Germany) was initiated, the day after allograft hepatectomy (12th POD) and continued for a total of 37 h (until the 14th POD, figures 1 and 2). The rationale for albumin dialysis was that it would provide additional detoxification in the anhepatic phase. After 43 h of anhepatic bridging (the 13th POD), the patient developed bilateral fixed, dilated pupils with an absence of reaction to light. The transcranial doppler ultrasonography demonstrated no impairment of cerebral perfusion. The clinical signs of cerebral oedema were immediately reversible using conservative treatment (mild hyperventilation, normothermia, barbiturate coma, osmotherapy with mannitol). CT or invasive intracerebral pressure (ICP) measurements were not used because of the patient's unstable haemodynamic and haemostatic situation. In addition, after 45 h of anhepatic bridging (13th POD), the patient developed a subendocardial myocardial ischaemia due to hyperdynamic circulation and metabolic disorder with progressive loss of systemic vascular resistance. A re-OLT was performed after a 56-h anhepatic bridging period on the 14th POD with an ABO-compatible whole liver (1000 g) from a

69-year-old brain death female donor (weight 50 kg; height 160 cm and BMI 20; AST 36 U/l, ALT 21 U/l; bilirubin 8.5 µmol/l; sodium 156 mmol/l and INR 1.2). The CIT and WIT were 421 and 36 min, respectively. An OLT was performed using above-described technique, followed by routine intraoperative Doppler ultrasound examination with flow values in the normal range.

After a re-OLT, anticoagulation was changed to argatroban (0.1–0.2 µg/kg/min) to achieve an acceptable activated partial thromboplastin time (aPTT). The overall transfusion demand including both OLTs was high (42 units of packed red cells). Transfusion for blood loss caused by severe hepatic coagulopathy was complicated by antierythrocyte antibodies (Duffy B). During the anhepatic period, we decided to allow a permissive anaemia with haemoglobin levels ranging from 5 to 7 mg/dl so long as the cardiac output and the central venous oxygen saturation were in an acceptable range. Our intention was to save the scarce resource of available compatible packed red blood cells for the anticipated re-OLT. But we were forced to abandon this plan owing to the occurrence of the symptoms of cerebral and cardiac organs failure.

During the postoperative period after a re-OLT, the patient developed pulmonary arterial hypertension (PAH) with a pulmonary artery systolic pressure of 51 mm Hg with a consecutive right heart failure and massive tricuspid insufficiency which was treated successfully with dobutamine, sildenafil and inhalative nitric oxide (NO).

ANTICOAGULANT THERAPY

When HIT type II was first diagnosed, anticoagulation was changed to the heparinoid danaparoid sodium, which was continued during the anhepatic phase.⁹ Danaparoid sodium works by inhibiting an activated factor Xa, and renal elimination is predominant. Drug monitoring is difficult using anti-Xa activity. Thus, the major disadvantages, especially in patients with renal dysfunction, are the dose monitoring difficulties caused by its long plasma half-life (24 h), and an increased bleeding risk. Argatroban,

Figure 3 Fulminant liver graft failure due to HIT type II-associated thrombotic complications: Top: fresh thrombotic material occluded a major branch of the portal vein (H&E stain, ×20), Bottom: predominant central vein bridging necrosis of the hepatocytes (H&E stain, ×20).

a selective and reversible direct thrombin inhibitor has been shown to improve outcome in patients with HIT.⁵ Argatroban is primarily metabolised in the liver and eliminated with a half-life of 39–51 min in healthy subjects through biliary excretion. Laboratory monitoring can utilise aPTT. Hepatic impairment is associated with a longer elimination half-life of argatroban, and drug accumulation with an increased bleeding risk is likely. However, there is no experience with argatroban in anhepatic patients; therefore, argatroban should not be used in this setting. Consequently, anticoagulation was switched to argatroban only after a re-OLT.

OUTCOME AND FOLLOW-UP

After a prolonged period of continuous haemofiltration (CVVH to the 19th POD), renal functions normalised. Three months after the OLT, including 30 days of ICU therapy, the patient had recovered cardiac function, normal liver graft function and excellent renal function and was discharged to a rehabilitation facility. Anticoagulation was switched to a coumarins derivative for 6 months. The patient remained in a good condition with excellent graft function 1 year after the OLT. He appeared intellectually unimpaired and denied any neurological deficits.

DISCUSSION

The use of UFH after the OLT is controversial especially because of possible complications due to HIT.^{6–7} There is no evidence that patients undergoing an OLT have a greater risk of developing HIT⁶, but in this cohort patients are more likely to be pre-exposed to heparin. We report a rare case of HIT type II after an OLT which caused severe hepatic and portal vein thrombosis with acute liver graft failure. It should be stated that, in the present case, clinically relevant right heart dysfunction with consecutive liver venous congestion, as well as liver packing, might have impaired blood flow through the graft and thus might have additionally predisposed to thrombosis of the hepatic and portal veins.

Initial reports of the two-stage procedure (total hepatectomy, temporary portacaval shunt and a subsequent re-OLT) indicated a high mortality mainly because patients developed lethal multiorgan failure within the first 34 h on the waiting list and suitable donor livers could not be allocated in time.³ But important efforts have been made by intensive care physicians and transplant surgeons to improve treatment of multiorgan dysfunctions and to prolong the anhepatic bridging period, and recent reports have shown more optimistic results with lower mortality.^{2–4} However, the reported anhepatic bridging periods were most often only between 10 and 34 h.^{3–4} In addition, reports of unsuccessful two-stage procedures without final graft allocation have rarely been published. The maximal time window of anhepatic conditions following allograft hepatectomy therefore remains unknown. One case report described a long-term survival after prolonged anhepatic conditions as part of a two-stage procedure of 67 h in an adult.²

Artificial and bioartificial support systems may assist bridging to an OLT.¹ Liu *et al*⁴ described successful two-stage procedures after primary graft dysfunction in two patients with anhepatic periods of 17 and 26 h with additional extracorporeal albumin dialysis. But there is still a lack of evidence showing superior patient outcome in randomised prospective studies to date.^{1–10–11}

High demand for transfusions during the OLT (≥ 20 units of packed red cells) or alloantibodies against erythrocyte antigens is associated with reduced long-time survival.¹² Therefore, permissive anaemia is recommended after an OLT. Here, maintaining a balance between permissive anaemia and the necessity of transfusion for an impaired coronary perfusion was crucial in the patient's outcome, but complicated by the evidence of antierythrocyte-antibodies (Duffy B). Limited availability of compatible erythrocyte concentrates caused additional logistic problems.

A major complication under anhepatic conditions is an elevated intracranial pressure (ICP) which leads to the loss of cerebral perfusion, cerebral herniation and irreversible brain damage in patients with ALE.¹³ In this case, invasive monitoring with an intraparenchymal ICP sensors was not possible due to persistent thrombocytopenia and severe hepatic coagulopathy, and hence intermittent transcranial Doppler sonography (TCD) was used for monitoring. Several groups have shown that the TCD waveform can be used to predict dynamic changes in ICP in a cohort of patients with ALE.¹³

Learning points

- ▶ Haemostatic and immunological monitoring and treatment are essential in patients undergoing an orthotopic liver transplantation (OLT).
- ▶ Heparin-induced thrombocytopenia type II is a very rare cause of early progressive liver graft failure.
- ▶ In acute liver failure or fulminant liver graft failure, a two-stage procedure (OLT after hepatectomy and anhepatic bridging) might reduce the systemic response to excessive liver cell necrosis.
- ▶ A prolonged anhepatic period (56 h) can successfully be bridged until the allocation of a suitable graft.
- ▶ Specific vital complications due to end-stage liver failure such as acidosis, coagulopathy, decreased vascular resistance, cerebral oedema or heart failure might limit this approach.

Acknowledgements We thank Björn Nashan, Director of the Department of Hepatobiliary and Transplant Surgery. His clinical and scientific expertise was very important for preparing this manuscript. We thank Florian Langer, Head of the Section Thrombosis and Haemostasis, Department of Internal Medicine II, Head of the Section, Thrombosis and Haemostasis, for his contribution towards questions about haemostasis and test methods. We thank Asmus Heumann, Department of Hepatobiliary and Transplant Surgery for his clinical contribution during the drafting of the manuscript and creation of the figures. We thank Alexander Quaas, Department of Pathology for preparing the micrographs of the liver.

Competing interests None.

Patient consent Obtained.

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Please cite this article as follows (you will need to access the article online to obtain the date of publication).

Pannicke N, Pollok JM, Kluge S, Petzoldt M. Heparin-induced thrombocytopenia associated with acute liver graft failure. *BMJ Case Reports* 2012;10:1136/bcr-2012-007323, Published XXX

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