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CASE REPORT

A case of acute humoral rejection in liver transplantation: successful treatment with plasmapheresis and mycophenolate mofetil

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Summary

We present a case of a 23-year-old female who underwent orthotopic liver transplantation (OLTx) for biliary atresia, 22 years after a failed Kasai operation. Unusually, her postoperative course was complicated by severe acute humoral rejection. In this case report, we discuss her management as well as the role of plasmapheresis in treating allograft dysfunction secondary to acute humoral rejection in liver transplant patients.

Introduction

Humoral rejection in orthotopic liver transplantation (OLTx) is a relatively uncommon phenomenon. This is primarily mediated by antibody and complement, occurring immediately (hyperacute) or during the first week (acute) after transplantation. The antibodies are either preformed or represent anti-donor antibodies that develop after transplantation [1]. There is some debate about the ability of lymphocytotoxic antibodies to cause clinically significant allograft dysfunction after liver transplantation [2].

Previous data published from our group suggested that those patients with either donor T or B lymphocyte directed IgG antibodies had a significantly increased incidence of clinical rejection when compared with those with no donor directed IgG. The differences were greater with B lymphocyte-directed IgG and were generally steroid sensitive [3].

We present a case of ABO compatible OLTx, which was complicated by acute humoral rejection in the presence of a positive T cell and B cell cytotoxic crossmatch. We were able to identify antibodies specific for target antigens on the transplanted organ. The patient recovered following treatment with plasmapheresis and immunosuppressive augmentation with steroids and mycophenolate mofetil.

Case presentation

A 23-year-old female was admitted for elective, first time OLTx for long-standing secondary biliary cirrhosis. At the age of 6 months, she had had a Kasai procedure for congenital biliary atresia and subsequently had problems with recurrent cholangitis, cholestatic pruritus and jaundice. She was transplanted with a whole liver graft of appropriate size, from a young donor. The cold ischemic time was between 12 and 15 h and the time zero biopsy showed changes suggestive of mild preservation injury only. Immunosuppression included: 500 mg of methylprednisolone administered intravenously at the time of reperfusion and maintenance was with triple therapy (Tacrolimus

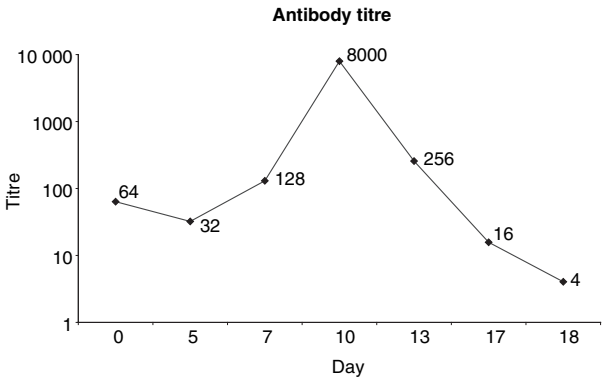

Figure 1 This graph demonstrates the immunological response following treatment.

0.1 mg/kg, Azathioprine 1 mg/kg and Prednisolone 30 mg) started on the first postoperative day.

On postoperative day 6, there was a marked deterioration in the patient's cardiovascular status with hypotension, oliguria, lactic acidosis and a decreased systemic vascular resistance, with a concomitant deterioration in liver function. Following a negative abdominal CT scan and no evidence of a confirmed nidus of sepsis, an exploratory laparotomy was undertaken. There was no gross evidence of intraperitoneal contamination, and an intraoperative color Doppler ultrasound confirmed good blood flow in the hepatic artery, portal vein and hepatic veins. A biopsy performed at laparotomy showed expansion of the portal tracts with an intense mixed inflammatory cell infiltrate with large numbers of plasma cells, eosinophils and blast cells. There was marked endothelialitis and endothelial cell swelling in some of the hepatic arterial branches. In some vessels, there were small fibrin thrombi. These appearances were consistent with severe acute cellular rejection with an overlay picture commonly associated with hyperacute humoral rejection (see Fig. 2).

A repeat crossmatch was performed, the positive result, which was present at the time of transplant (1:64) was confirmed, but the donor-specific antibody titer was lower (1:32), probably due to antibody adhering to the graft. This was followed by a massive increase in the donor-specific antibody titer to 1:8000 (see Fig. 1).

Due to the rapid nature of the deterioration, she was treated with i.v. steroid augmentation, plasmapheresis (seven courses) and 100 mg/kg of human normal i.v. immunoglobulin. High dose mycophenolate mofetil (MMF 1.5 g bd) was also substituted for azathioprine and tacrolimus was continued, maintaining a trough level of 7.5–15 mg/ml. With this treatment, there was a marked improvement in liver function (see Table 1), a dramatic fall in the lactate from a peak of 11.5 mmol/l and a fall in the donor-specific antibody titer (see Fig. 1). Further analysis of the pretransplant serum using Luminex antibody screening assay revealed specificity for HLA Bw6, an epitope expressed by both B7 and B61 donor antigens, however, after plasmapheresis only donor-specific B7 antibodies could be seen. The tissue types of the two patients were as follows:

Recipient – HLA-A2, B44 B51, Cw5 Cw15, DR4 DR12 DQ7 DQ8.

Donor – HLA-A31 A33, B7 B61, Cw7 Cw15, DR10 DR14 DQ5.

The diagnosis of antibody-mediated rejection was assisted by detection of specific IgG antibodies directed against specific graft antigens detected by Luminex technology. Luminex technology uses solubilized HLA molecules bound to microparticles and therefore antibodies detected are specific for HLA antigens. Retrospective crossmatching was performed on fresh donor splenocytes within 24 h of transplant. There was never any evidence of class II antibodies by Luminex, however, the B cell crossmatch was positive due to class I antibodies.

The patient was discharged to the ward on postoperative day 18, and continued to make steady progress until she was discharged home.

Retrospective C4d staining was carried out on paraffin embedded tissue taken at the time of laparotomy. The result of this was equivocal.

At 14 months, the patient had not suffered any episodes of decompensation, and repeat serology did not

Table 1. This demonstrates the biochemical recovery following treatment.

Post of day	4	5	6 (am)	6 (pm)	7	8	9	10	11	12
Intervention					Plasmapheresis + steroids started			MMF started		
PT secs	16	16	16	20	21	20	18	17	16	15
Albumin g/l	26	26		18	24	29	31	28	25	30
Bilirubin μmol/l	179	174	181	181	155	194	171	193	218	170
Alk Phos IU/l	206	193	181	183	105	121	93	88	121	93
ALT IU/l	960	1061	1126	1460	971	963	489	259	231	86

detect any antibodies against HLA antigens by Luminex or ELISA techniques.

Discussion

By tradition, early rejection in solid organ transplantation has been divided up in to hyperacute and acute rejection. It is believed that the mediator of hyperacute rejection is humoral immunity, whereas that of acute rejection is cellular immunity.

Hyperacute rejection is seldom a problem in liver transplantation and this is probably due to the avoidance of crossing the ABO blood groups. In acute rejection, most tissue damage is thought to occur as a direct result of cellular injury to bile duct epithelium. Acute rejection episodes are accompanied by an upregulation in the expression of HLA class I antigens on hepatocytes and HLA class I and II antigens on vascular endothelium, but it is unclear as to whether this is the cause or result of acute rejection [4]. More recently, it has been realized that humoral immunity also plays a role in acute rejection [5]. A recent study showed that preformed biliary epithelial cell reactive antibodies have a detrimental effect on liver allografts, and in some cases these are directed against HLA antigens [6]. However, antibodies directed at antigens expressed on the vascular endothelium are potentially the most destructive, since vascular injury interferes with the blood supply [1]. In hyperacute, immediate humoral rejection (Fig. 2) preformed antibodies reactive against the major ABO blood group or class I MHC antigens expressed on the graft are responsible and are detectable in conventional blood typing and lymphocytotoxic crossmatch tests. Indeed, this was the case in our patient who had antibodies specific for the donor's HLA class I antigens.

Although the risk of developing acute rejection is increased in those patients with a high panel reactive antibody, the logistical problems with allocation outweigh the benefits of prospective crossmatching [7]. In our patient, 6 months previously, there was a negative antibody screen and no evident sensitizing event. However, it is possible that a nondescribed sensitizing event may have occurred leading to a positive crossmatch.

The liver is thought to be largely resistant to humoral rejection and this may be related to secretion of soluble HLA class I antigens by the liver [8], Kupffer cell phagocytosis of cytotoxic antibodies and complement [9]. The complement-mediated lysis of target cells may be less effective if the target cell and complement are derived from the same source, thus by providing syngeneic complement, the liver may protect itself against complement-mediated lysis triggered by preformed antibodies [9,10]. These factors may have delayed the clinical onset of antibody-mediated rejection in our patient. However, a major risk factor for humoral rejection in our case could have been the high antibody titer at the time of transplantation (1:64).

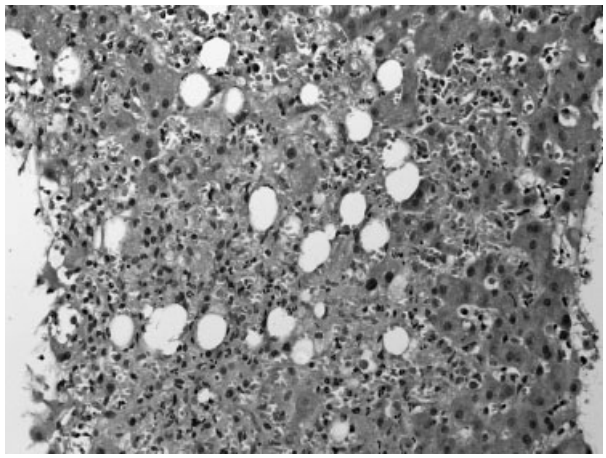

Figure 2 Confluent liver cell necrosis and congestion in perivenular zones (features of humoral rejection). H&E.

In kidney transplantation, successful management of antibody-mediated rejection is dependent on standardized diagnostic criteria. Serology, histology or immunohistochemistry if applied individually may be insufficient and thus it is thought that a combination of all three diagnostic procedures could compensate for insufficient sensitivity or specificity of any individual technique [11].

Plasmapheresis has been shown to be an effective method of reducing rejection in ABO-incompatible liver transplants [12] and living-related liver transplants [13]. The success of this is dependent on its preoperative use removing or reducing antibody titer prior to transplant. We were able to demonstrate its effective use in reducing the antibody titer against a known target. In addition, we employed mycophenolate mofetil to impair B cell-mediated proliferation by its inhibition of the isoform of the enzyme inosine monophosphate dehydrogenase. A study into the treatment of acute humoral rejection in renal transplantation has shown that a similar therapeutic approach combining plasmapheresis, tacrolimus and mycophenolate mofetil has the potential to improve outcome [14].

Therefore, severe rejection after OLTx, in the presence of a positive crossmatch, can be successfully managed by plasmapheresis and augmentation of immunosuppression.

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