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BRIEF REPORT

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Successful management of hemolysis in ABO-nonidentical orthotopic liver transplantation by steroid therapy: a case report

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Abstract Hemolysis due to donor-derived B lymphocytes has been reported in patients who have undergone ABO-nonidentical orthotopic liver transplantation (OLT). Yet, until now, little was known about the management of this transplantation-induced hemolysis. In this report we describe our experience with hemolysis in a patient after OLT. In addition, based on theoretical assumption, we hypothesize that corticosteroids can be helpful in the management of ABO-nonidentical OLT-induced hemolysis.

Key words Liver transplantation, hemolysis, corticosteroids · ABO-nonidentical, liver transplantation, corticosteroids · Hemolysis, liver transplantation · Corticosteroids, hemolysis, liver transplantation

Introduction

Due to the limited supply of livers for transplantation and the sometimes acute situation in which an orthotopic liver transplantation (OLT) is needed, nonidentical ABO blood group OLTs are regularly performed; in fact, they account for 10 %–35 % of all OLTs performed [8, 20]. The liver is considered to be an immunologically privileged organ with a relatively low risk of hyperacute rejection when transplanted across nonidentical ABO blood groups. However, one of the risks of transplanting an O liver into an A/B/AB recipient is the development of isohemagglutinins against the recipient by donor-derived lymphocytes [2, 14–16], which may induce hemolysis. Substantial morbidity has been reported in association with hemolysis, including acute renal failure, disseminated intravascular coagulation, hypotension, and multiorgan failure causing death [1, 6, 10, 20].

Whether changes in a given therapeutic regimen can prevent or reduce the incidence of isohemagglutinin-induced hemolysis is not yet known. Based on theoretical assumptions concerning the effects of steroids, such as inhibiting the release of lysosomal enzymes and impairing interleukin-1 transcription, we hypothesized that steroids might be helpful in the management of this iso-

hemagglutinin-induced hemolysis. In this report we describe our experience with an ABO-nonidentical, OLT-induced hemolysis in a patient.

Case report

A 46-year-old man (blood type B, Rh-D-positive) who was suffering from decompensated cirrhosis due to chronic hepatitis C infection (HCV-RNA-positive, Child Pugh score C) received a liver allograft from a type O (Rh-D-positive, HLA-ABC-DR-unmatched) donor. Preoperative laboratory studies showed the following: SGOT 97 U/l, SGPT 97 U/l, serum bilirubin 26 mmol/l, PT 13.5 s, serum LDH 216 U/l, leukocyte count 13×10^9/l. During the operation the patient was given 20 units of packed red blood cells (type B), 2000 ml of geloplasma, 19 units of fresh frozen plasma (type B), and 20 units of type B platelets. Immunosuppressive therapy consisted of a triple-drug regimen of steroids, cyclosporin, and azathioprine. On days 4–6, Solu-Medrol (1000 mg/day) was given because a liver biopsy showed signs of rejection (Snoover II). Hemolysis occurred postoperatively on the 10th day (Fig. 1). Simultaneously, serum LDH increased (Fig. 2). Serum Hb continued to drop despite blood transfusions (four units of packed red blood cells, type B) on the 11th and 12th postoperative days. On day 13 the direct antiglobulin test was positive for anti-IgG, and the specificity of the antibody was found to be anti-B. During the hemolytic period, peripheral blood cell differentiation showed an increased number of reticulocytes. In addition, bone marrow aspiration revealed an accelerated erythropoiesis, thrombopoiesis, and myelopoiesis. The peripheral blood cell count revealed a leukocytosis with a maximum value of 59×10^9 on the 14th postoperative day (Fig. 2). From that moment on, only donor type O packed red blood cells were used to correct the anemia, and the corticosteroid dosage was increased from 25 mg/day to 100 mg/day (Fig. 1). After reducing the steroid dosage to 25 mg/day on the 21st postoperative day, hemolysis again occurred. This hemolytic period could be adequately treated with donor type O blood transfusions (two units) and by temporarily increasing the steroid dosage.

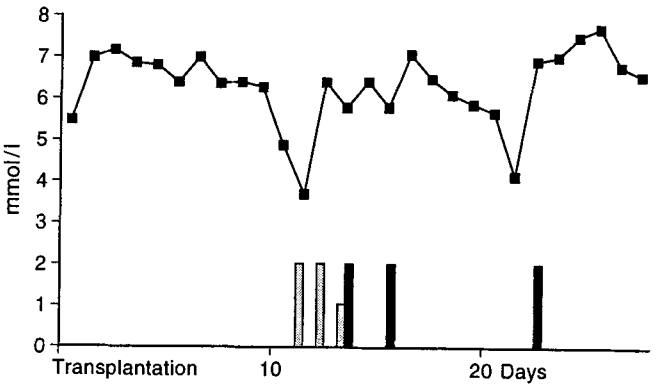

Fig. 1 Blood hemoglobin level after transplantation. Note the two hemolytic periods requiring blood transfusion. ▒ B-positive; ■ O-positive; ■—■ hemoglobin

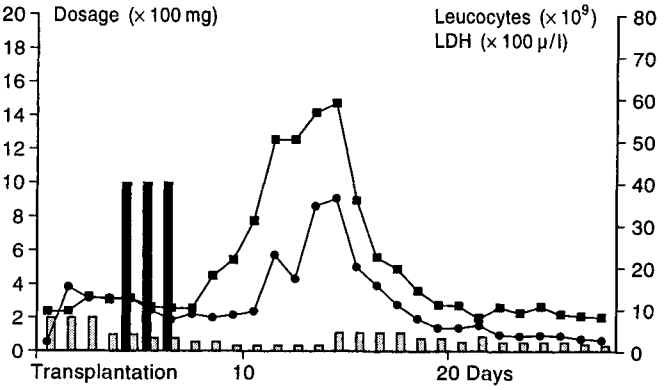

Fig. 2 Serum LDH and blood leukocyte count after transplantation. Note the increase during hemolysis and the decrease after increasing steroid therapy. ■ Solu-medrol; ▒ corticosteroid; •—• LDH; ■—■ leucocytes

Discussion

In 1971, Beck and colleagues were the first to describe the passive transfer of viable lymphocytes with the capability of producing antibodies [3]. Since allotyping has demonstrated the donor origin of these antibodies [6, 15], the concept of graft-derived antibodies from passenger lymphocytes being directed to host antigens after solid organ transplantation has been widely accepted. The incidence of these antibodies correlates with the size and lymphoid content of the transplanted organ [2]. A liver graft usually contains mononuclear donor cells that are 10 %–40 % granulocytes, 20 %–30 % monocytes, and 35 %–70 % lymphocytes. The lymphocytes are located in either the sinusoids of the liver tissue (mainly $CD4^-$, $CD8^+$ T cell and NK cell type) or the lymph nodes (mainly $CD4^+$, $CD8^-$ T cell and type B cell) [9, 19]. Most donor B cells are thus derived from lymphoid tissue transplanted together with the liver and contain some $20–500 \times 10^6$ lymphocytes that are not from the liver itself, while the liver contains far more (10^9–10^{10}) lymphocytes [9, 19]. B lymphocytes are capable of producing isohemagglutinins that can induce alloimmune hemolysis [15]. Circulating and red cell-bound isohemagglutinins can be detected from day 8 to day 16 post-transplantation. This 8 to 16-day latency and the frequently observed IgG component of these antibodies are consistent with a secondary immune response from previously primed donor B lymphocytes [18]. Therefore, the passive transfer of antibodies from the liver itself or through blood transfusion can be considered negligible. The antibodies can circulate for up to 6 months after transplantation, and only O grafts have been reported to produce anti-A or anti-B antibodies in an unmatched recipient [20, 21].

Theoretically, hemolysis can occur in all ABO-nonidentical patients. In a review article, however, Ramsey reported an overall 40 % incidence of antibody detection and 29 % incidence of hemolysis in ABO-noniden-

tical liver transplant recipients [14]. Other reports suggest an even higher incidence [1, 10, 23]. Reliable parameters that may be helpful in predicting which patients will develop red cell antibodies or hemolysis have not yet been established [23]. When these antibodies are present, hemolysis has been described to occur in the 2nd week after transplantation; in our patient, hemolysis was observed on day 10. Blood transfusions (type B) were given on the 11th and 12th postoperative days and hemolysis continued. As expected, serum LDH continued to increase and reached maximum values at day 14. By that time, the direct antiglobulin test was positive (anti-IgG type) with anti-B antibodies detectable in serum. Because hemolysis continued, the steroid dosage was increased in an attempt to reduce B-cell activation and antibody production. Red cells of donor type O were given from day 13 on and hemolysis stopped. There was no evidence of infection, so the leukocytosis was interpreted as secondary to general bone marrow activation. A second hemolytic period occurred after the steroid dosage had been tapered to 25 mg/day and could be adequately dealt with by temporarily increasing the steroid dosage and using donor type red blood cells. The direct antiglobulin test was negative on day 22. The further postoperative course was uneventful and the patient was discharged from the hospital on the 34th postoperative day.

Just why the increase in the steroid dosage reduced hemolysis in our patient can only be speculated. Until now there has been little evidence that the immunosuppressive drugs given after transplantation can reduce the incidence or duration of hemolysis in ABO-nonidentical OLT patients [11, 14]. There are, as yet, no means of influencing the activation of the complement system by these alloreacting antibodies [7]. Furthermore, steroids and cyclosporin are known to have relatively little effect on the secondary responses on antigen presentation to B cells [11], and on the duration of circulating antibodies [4]. However, corticosteroids can inhibit the release of lysosomal enzymes by monocytes/macrophages and inhibit cytotoxic lysis [7], as shown in serum autoantibody-mediated destruction. A long-term effect of corticosteroids is the reduction in antibody synthesis [17]. Another possible explanation for the reduced hemolysis may be the influence of steroids on lymphokine production. During antigen presentation, different types of lymphokines are produced. One of these is interleukin 1 (IL-1), which is thought to play an important role in T-cell proliferation and activation [5, 11]. Corticosteroids impair transcription of the IL-1β gene [22], cause rapid degradation of IL-1 m-RNA [12], and reduce IL-6 transcription [24], thereby inhibiting the generation of the costimulatory signal [13, 22]. We believe that through one or more of these mechanisms, steroids can be helpful in the management of hemolysis in ABO-nonidentical OLT patients. The management of the donor-induced hemolysis described in this report may support this concept.

We conclude that in the case of an ABO-nonidentical OLT, it is advisable to use recipient type blood components initially and to monitor the patient for antirecipient ABO antibodies. If they appear, donor type, or even O type, red cells should be given when needed throughout the period when the antibody is present. Although one can only speculate on the role played by changes in the immunosuppressive regimen, we believe that corticosteroid therapy may be helpful in suppressing hemolysis. Because ABO-nonidentical, OLT-induced hemolysis appears to be a self-limiting disease, changes in transfusion strategy, as well as in corticosteroid therapy, are probably only necessary in the 1st few postoperative weeks.

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