TRANSPLANT INTERNATIONAL

LETTER TO THE EDITORS

Successful ABO-incompatible kidney transplantation in patient with congenital afibrinogenemia

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Dear Editors,

Congenital afibrinogenemia is a rare coagulation disorder with an estimated prevalence of 1 in 1 million. Fibrinogen plays an important role in clot formation through its conversion to fibrin by the action of thrombin and is also involved in normal wound repair. Fibrinogen replacement therapy is the only treatment for bleeding episodes in affected patients. However, that therapy elevates the risk of thrombosis. Herein, we report successful ABO-incompatible kidney transplantation in a patient with congenital afibrinogenemia.

A 33-year-old male was diagnosed with congenital afibrinogenemia shortly after birth and treated with fibrinogen replacement therapy when bleeding episodes occurred. End-stage renal disease caused by unidentified chronic glomerulonephritis was a comorbid condition, and continuous ambulatory peritoneal dialysis (CAPD) and hemodialysis (HD) were required from the age of 32. He had been given fibrinogen during each HD session for hemostasis. The patient, blood type A, underwent ABO-incompatible living related kidney transplantation in January 2009 from his father, who was blood type AB. Pretransplant anti-B agglutinin titers were 1:4 for IgG and 1:4 for IgM.

Human leukocyte antigen (HLA)-A, -B, and -DR typing showed one identical haplotype. Pretransplant T- and B-cell cross matching using complement-dependent-cytotoxicity and flow cytometry cross-match were negative.

The pretransplant desensitization regimen consisted of mycophenolate mofetil, and methylprednisolone started at 14 days before transplantation, cyclosporine for 3 days, two doses (each 100 mg/m^2) of rituximab (RIT) was given 14 and 7 days, respectively, before transplantation, and two sessions of double filtration plasmapheresis. The fibrinogen replacement therapy started at 1 day before transplantation in addition to each HD session. On the day of transplantation, anti-B agglutinin titers were decreased to 1:<1 for IgG and 1:1 for IgM, thus it was considered to be safe to perform. The CAPD catheter was removed before the procedure. The total operation time was 11 h 25 min, and total and warm ischemic times were 135 and 7 min, respectively. Estimated blood loss was 570 ml. One week after transplantation, the level of serum fibrinogen was controlled above 100 mg/dl by fibrinogen replacement therapy (Fibrinogen HT i.v. Benesis®, Benesis Corporation, Osaka, Japan) and anti-coagulation therapy was started concurrently on day 1. Although a ureteral stent was inserted because of urinary leakage, no other wound repair problems, abnormal bleeding, or thrombosis was observed during the post-transplant course with fibrinogen replacement and anti-coagulation therapy. The clinical course of the patient is detailed in the Figure. The ureteral stent was removed on postoperative day 34 following disappearance of urinary leakage. Protocol graft biopsies were performed safely on the day of and 8 months after transplantation with fibrinogen replacement. The biopsy specimen had normal findings. At 15 months after transplantation, graft function was stable, with a Cr level of 1.7 mg/dl and fibrinogen replacement therapy being administered once or twice a month. Anti-B agglutinin titers were stable to 1:4 for IgG and 1:4 for IgM.

Congenital afibrinogenemia, first described by Rabe in 1920 [1], is a rare bleeding disorder with an estimated prevalence of 1 in 1 million. The disease is characterized by the complete absence of fibrinogen production by a mutation in genes that encode the polypeptide chains of fibrinogen. The condition is considered to be inherited as an autosomal recessive trait, and is characterized by bleeding events that often start at birth with uncontrolled umbilical cord hemorrhaging. Bleeding may also occur after a scarcely noticed trauma or small intervention into the skin, mucosa, muscle, or brain, with the latter often fatal. This is the first report of kidney transplantation in a patient with congenital afibrinogenemia, who was diagnosed at birth from umbilical cord hemorrhaging.

Fibrinogen plays an important role in clot formation through its conversion to fibrin by the action of thrombin as well as in normal wound healing, with reports of wound healing following surgery [2]. Fibrinogen replacement therapy is effective for treating bleeding episodes in congenital afibrinogenemia, in which the patient receives fresh frozen plasma (FFP), cryoprecipitate, or fibrinogen concentrate. Fibrinogen concentrate is the treatment of

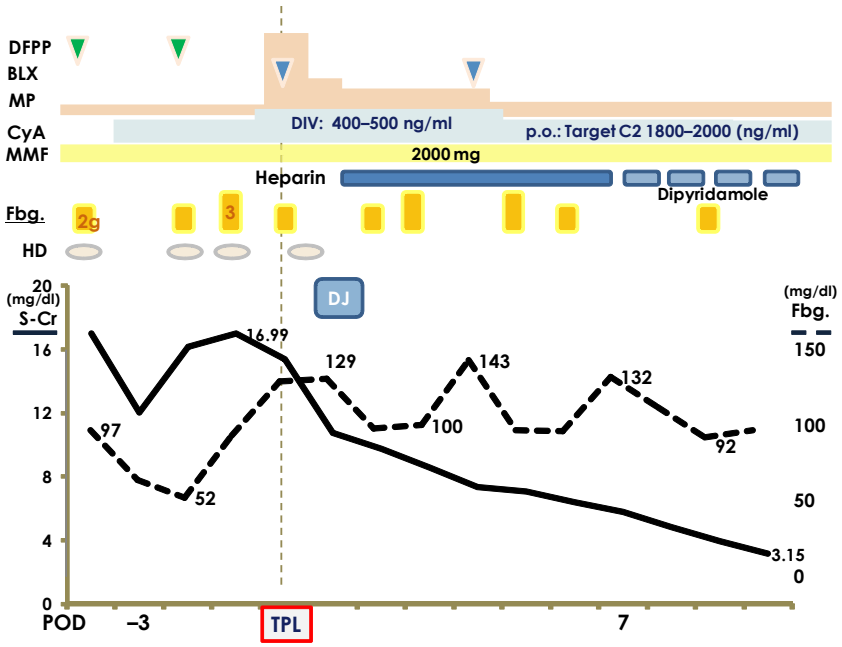

Figure. Clinical course of peritransplant.

choice because it is safer than cryoprecipitate or FFP, and includes safety steps for removal and inactivation of viruses [3] and reduces the risk of thrombotic complications.

According to the UK guidelines for therapeutic products for coagulation disorders, in cases of bleeding, surgery, and pregnancy prophylaxis serum fibrinogen levels should be increased to 100 mg/dl and maintained above this level until wound healing is complete [4]. The half-life of fibrinogen concentrate is about 4–5 days, thus fibrinogen replacement therapy is generally given weekly until wound healing. In the present patient, the serum fibrinogen level was increased to 100 mg/dl and maintained above that level until 1 week after surgery, which effectively prevented abnormal bleeding and delayed wound repair.

Thrombotic complications have been reported in patients with afibrinogenemia following replacement therapy, including deep vein thrombosis and pulmonary embolism [5,6]. The risk might be greater when cryoprecipitate and FFP are used as compared with fibrinogen concentrate because the latter contains substantial quantities of other coagulation factors [7]. Fuchs *et al.* [8]. reported liver transplantation in a patient with congenital afibrinogenemia complicated by Budd-Chiari syndrome as a reason for replacement therapy with cryoprecipitate. Furthermore, De Mattia *et al.* [9]. proposed concomitant administration of replacement therapy with anti-coagulation therapy for management of thrombotic complications. In the present patient, we administered heparin as anti-coagulation therapy and fibrinogen replacement therapy.

Fifteen months after the operation, graft function was stable with Cr at 1.7 mg/dl. Replacement fibrinogen therapy is being continued once or twice a month, with nasal or oral mucosa oozing sometimes noted. A few reports have described the appearance of anti-fibrinogen antibody in afibrinogenemia patients receiving frequent replacement therapy [10], which will need to be monitored.

This is the first report of successful kidney transplantation in a patient with congenital afibrinogenemia. Maintenance of perioperative serum fibrinogen level with fibrinogen replacement therapy and appropriative anti-coagulation therapy were considered to be important for a safe clinical course.

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Conflicts of interest

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