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Disseminated Intravascular Coagulation (DIC) Accompanied by Acute Rejection in a Post Renal Transplant Recipient*)

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ABSTRACT

A kidney transplant recipient with disseminated intravascular coagulation (DIC) accompanied by acute rejection was described. The principal symptome of the patient was massive gross hematuria. She showed thrombocytopenia, marked decrease of fibrinogen and elevation of fibrinogen degradation products (FDP) level. The patient was treated by continuous intravenous heparin infusion (total dose was 85, 800 units), and it was very effective. The symtoms due to DIC were improved on the 9th day after the begining of heparin therapy.

INTRODUCTION

Disseminated intravascular coagulation (DIC) is a syndrome with bleeding diathesis due to consumption of platelets, fibrinogen and other clotting factors during intravascular coagulation. DIC is always accompanied by basic disease, which causes DIC. Malignant tumor and severe infection are the typical diseases related to DIC[9]. Although rejection in organ transplantation is also a pathogenic situation, which possibly causes DIC, there were few reports of clinical cases in kidney transplantation. In this study, a living related kidney transplant patient, who developed DIC after acute rejection, was discussed.

PATIENT

This patient was a 30 years old of female. She was taken in pyelonephritis at 20 years old. When she was 24 years old, she conceived a second child and was diagnosed as gestational toxicosis because of marked albumin uria. Then she underwent an artificial abortion. Albumin uria had been continued after that. When she was 29 years old, she had general tiredness and edema. Then she was diagnosed as chronic renal failure, and treatment by hemodialysis was started.

Nine months after the begining of hemodialysis, she came to our department in order to have a living related kidney transplantation. Kidney donor was her mother. HLA compatibility was C match and MLC was moderate response (S. I.: 8. 3, Double Normalized Value: 52. 9%). A total of 14 units of blood were transfused from random donors and 200 ml of donor blood was transfused one day before transplantation. Laboratory data on the patient before operation were shown in Table 1. There was no abnormal findings on thrombocyte number, clotting system and liver function. Clinical course of the patient was shown in Fig. 1. Left kidney of the donor was grafted to the patient. Four min after reflow through renal artery, initial urination was observed.

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Table 1. Laboratory data before operation

Peripheral blood		Liver function test	
WBC	4700/mm³	Total Protein	6.4 g/dl
RBC	218×10⁴/mm³	A/G ratio	1.67
Hb	6.4 g/dl	S-GOT	5 Unit/liter
Hct	19.2%	S-GPT	4 Unit/liter
Plat.	28.2×10⁴/mm³		
Blood coagulation test			
Prothrombin time	11.6 sec		
(control	11.0 sec)		
Fibrinogen	195mg/dl		
FDP	2.5 mg/dl		
Bleeding time	3.5 min		
Clotting time	14.0 min		

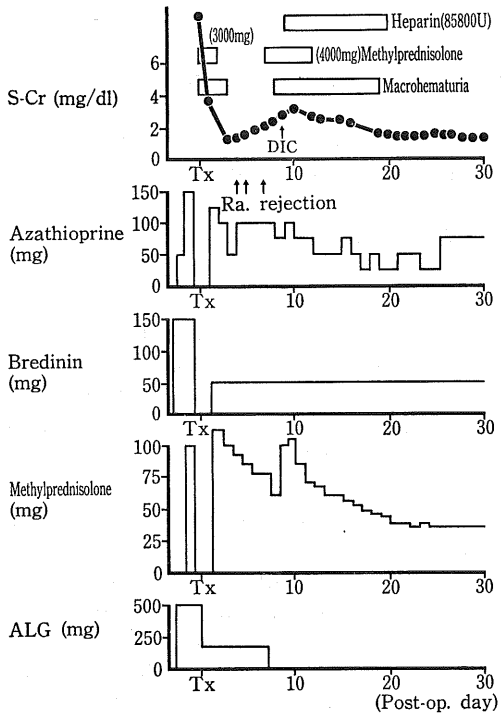

Fig. 1. Clinical course of the patient

Immunosuppressant of this patient was as follows: Bredinin was given from three days before operation, and azathioprine and methylprednisolone were given two days before it. Anti-lymphocyte-globurine (ALG) was given for two days just before transplantation and for seven days after that. Ooze from the operative wound was observed during the operation. It was considered to be due to decrease of thrombocyte by ALG, and the administration dose of ALG was reduced from 500 mg/day to 200 mg/day. Mild hematuria was observed for three days after operation, but it improved with no treatment. Although serum creatinine smoothly decreased, it gradually increased from 5th day after grafting. The serum creatinine level elevated to 3.5 mg/dl, and the patient was diagnosed as undergoing acute rejection. High dose of methylprednisolone was intravenously infused as anti rejection therapy. On the eighth day after operation, massive gross hematuria occured. Bleeding time was more than 30 min and clotting time was more than 2 hr. Therefore administration of ALG was stopped. In precise examination of the clotting system system, prothrombin time delayed to 15.2 sec, fibrinogen increased to 39 mg/dl, FDP also increased to 20 μg/ml. Moreover thrombocyte number decreased to 8×10^4/mm³. According to such data, the cause of massive hematuria of this patient was diagnosed as a symptom of DIC. Thus continuous infusion of heparin was began immediately. After the first intravenous injection of 1000 unit of heparin, continuous infusion was began at 250 unit per hr, and increased to 600 unit per hr. The dose of heparin was decided by the data of activated partial thromboplastin time (A-PTT). Total dose of heparin in this patient was 85,800 units. Change of laboratory data was shown in Fig. 2. Although the thrombocyte number decreased to 1×10^4/mm³ on the second day after the beginning of heparin therapy, it gradually increased after that. Fibrinogen and FDP levels were also rapidly restored. Serum level of anti-thrombin III was slightly low (25 mg/dl). Gross hematuria had completely improved on ninth day

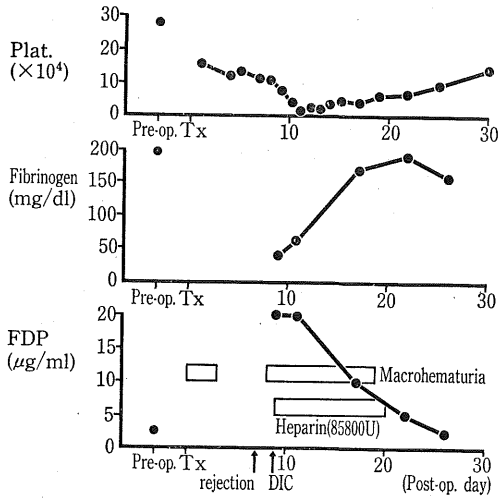

Fig. 2. Change of platelet, fibrinogen and FDP before and after heparin therapy

after the begining of heparin infusion, and renal function of the graft restored to normal. Thus the DIC of the patient ceased altogether. There was no liver function disorder during the DIC episode.

DISCUSSION

In 1970, Simpson et al.[13] obtained hyperacute or accelerated rejection in kidney transplantation in mongrel dog from sensitization with repeated skin graft. They reported that coagulopathy existed inside of the graft, and some cases developed DIC. In the same year, Starzl et al.[14] reported two cases of DIC accompanied by hyperacute rejection in kidney transplant patients. One patient already had cytotoxic antibody against donor cells before grafting. Generalized ooze in the operative wound occured. This bleeding diathesis was diagnosed as a symptom due to DIC. The bleeding could not be controled in spite of heparin therapy. The transplant developed anuria in five days, and it was removed after 13 days. Another case did not have detectable preformed humoralanti bodies. This patient fell into anuria 36 hr after grafting. As urine flow diminished, multiple clinical signs of serious bleeding diathesis occured, including hematuria, epistaxis, subconjuctival hemorrhage and upper gastrointestinal bleeding. The patient died approximately 4 days after the operation.

Although DIC accompanied by hyperacute rejection in kidney transplant patients was well known, there were no reports about DIC following acute rejection. Multiple thrombosis in grafted tissue might rarely occure even in acute rejection. In such a situation, it possible that DIC develope. The mechanism of DIC in asute rejection was described as follows. Endotherial cells of blood vessels, which had histocompatibility antigen, were destroyed by both effector cells and allo-antibody[4,11]. Thus, basement membrane and collagen were exposed into the lumen of the vessel. This brought fixing and clumping of thrombocytes, and activated factor XII[12].

In organ transplantation, thrombosis occurs in the graft and DIC is mild in most cases. Minna et al.[10] called this phenomenon as local DIC and distinguished it from generalized DIC. In our case, local DIC occurred, accompanied by acute rejection, and activation of the clotting system was so strong that the local DIC developed to generalized DIC. On the other hand, the thrombocyte number decreased during ALG therapy had been done. This might be slightly related to DIC. But there was no clear evidence on this point, because the admi nistrated dose of ALG was not too much.

There were various criteria concerning the DIC. According to the Matsuda's criteria[8], the score of this patient before heparin therapy was five. This value indicated DIC. In any other criteria, this patient was in DIC. Clinical symptoms of DIC include bleeding diathesis and organ failure resulting from circulation disturbance due to thrombosis. Characteristic symptom of this patient was massive gross hematuria, and there were no other massive bleeding. The frequency of macroscopic hematuria was 32% (by Minna[10]) or 10% (by Matsuda[8]). The most usual bleeding symptom was prupula or ecchymosis, and the frequency of these were 63% according to Minna's report[10]. Our patient showed them four days after the diagnosis as DIC. The most effective treatment for DIC is to cure the disease, which caused DIC. The cause in our patient was considered to be acute rejection. Pulse therapy of steroid was therefore done for treatment of acute rejection. Next relevant treatment is heparin therapy. It is generally accepted that the action of heparin is the inhibition of clotting through marked acceleration in connecting anti-thrombin III to thrombin and activated

fator X. Therefore the sufficient presence of anti-thrombin III in blood was needed for heparin to have a good effect. Moreover liver function should be normal, because antithrombin III is produced in liver. Liver function of this patient was not impaired and her serum level of anti-thrombin III slightly decreased to 25 mg/dl. Thus, successful effect of heparin could be expected. Continuous intravenous infusion is the most effective method for administration of heparin, because the half life of heparin in circulation is very short. Some authors[5,6,10] described that relatively high dose (18,000–16,000 units per day) was effective, but several other authors[2,3] reported that even though relatively low dose (6,000–10,000 units per day) was effective. Recently, it has been appreciated to give relatively low dose or to give low dose at the beginning of heparin therapy and to increase it gradually. Clotting time or prothrombin time were usually used as the basis to decide the administration dose of heparin, but we used A-PTT as the bases in this patient, because A-PTT is a very easy test and it needs short time to examine. Heparin therapy should be done during A-PTT is less than 45 seconds.

This patient has been maintaining good graft function for three years after transplantation and altogether come back to her normal usual life.

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