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CLOTTING CHANGES, INCLUDING DISSEMINATED INTRAVASCULAR COAGULATION, DURING RAPID RENAL- HOMOGRAFT REJECTION*

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Abstract

One of two patients in whom early homograft rejection developed after renal transplantation had many antidonor antibodies before operation. By the measurement of gradients across intracorporeal and extracorporeal homografts in this patient, the new kidneys were shown to sequester host immunoglobulins, platelets, white cells and clotting factors. Moreover, the renal venous blood then contained fibrinolytic activity. This presensitized recipient, as well as a second patient who did not have detectable preformed humoral antibodies, gave evidence from clinical observation and from the various clotting tests of disseminated intravascular coagulation with fibrinolysis and a severe bleeding, diathesis. Immunofluorescent and histologic studies revealed a laying down of fibrin in the homograft vessels that continued in some cases to cortical necrosis of the transplanted kidneys or, alternatively, receded at the time fibrinolysis occurred. The variety of rejection seen in these patients has been characterized as an immunologically induced coagulopathy.

When a kidney homograft is revascularized in a recipient who is presensitized to donor antigens there is a substantial risk of either accelerated or hyperacute rejection of the transplant.¹⁻⁵ The mechanism of the immediate destruction has been disputed. Two years ago in this journal, a clinical report from our institutions⁵ suggested that an instantaneous antigen-antibody reaction or other mechanisms could precipitate a coagulopathy like that of the Shwartzman reaction and that the consequent fibrin thrombi could occlude the renal micro-vasculature and be responsible for cortical necrosis. The principal evidence in support of this contention was from special histologic examinations. Unfortunately, clotting assays were not obtained in these patients.

A subsequent publication by Colman and Merrill and their associates confirmed that there were massive fibrin deposits in two human kidneys that had been hyperacutely rejected by apparently presensitized recipients.⁶ However, no systemic clotting changes could be detected in either of their patients, nor was there an arteriovenous gradient of any of the measured coagulation factors across the kidney in the most completely studied of these cases. Because of the negative findings, there was no satisfactory explanation even for the local intravascular coagulation that the authors postulated and no evidence whatever that there had been a systemic clotting disorder at any time.

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In contrast, studies from our laboratories have shown that noteworthy alterations in local or systemic coagulation regularly occur in presensitized dogs after the transplantation of the kidney, liver or spleen.⁷ The same thing has been seen in two recently treated patients whose renal homografts failed promptly. In both these human recipients, studies obtained revealed consumption of clotting factors either within the kidney or systemically, as well as fibrinolysis and a bleeding diathesis.

Methods

The techniques of renal transplantation and postoperative care were standard.⁸ Immunosuppression was with azathioprine, prednisone and intramuscular horse antilymphocyte globulin (ALG).⁹

Immunologic Studies

Tissue typing of the donors and recipients was carried out both in Denver and by Dr. Paul Terasaki in Los Angeles with the use of a serologic method.¹⁰ In addition, preformed leukoagglutinins,¹¹ lymphocytotoxins¹² and heterohemagglutinins against sheep red blood cells¹³ were looked for in the serums of the recipients. With a mixed agglutination test,¹⁴ Professor Felix Milgrom, of Buffalo, New York, examined these serums against Hela and HEp-2 cell lines.

When performed antibodies were found in Patient 1, the serum was fractionated with diethylaminoethanol (DEAE) cellulose column chromatography with the use of gradient elution.¹⁵ The fractions were identified for immunoglobulin class by immunoelectrophoresis.¹⁶ In the fractions, the presence or absence of leukoagglutinins, lymphocytotoxins and heterohemagglutinins was determined. Quantitative determination of IgG was performed with a commercial immunoplate.^{*17}

Hematologic and Coagulation Studies

Hematocrit, white-cell counts and platelet counts¹⁸ were assayed in blood anticoagulated with ethylene diamine tetra-acetic acid (EDTA).

Platelet-poor plasma was obtained by mixture of 9 parts of blood with 1 part of anticoagulant (3 parts 0.1 M sodium citrate, 2 parts 0.1 M citric acid) and centrifugation for 20 minutes at 4°C and 4000 rpm. The following tests were done in fresh plasma: euglobulin lysis time¹⁹; thrombin time with 5 U per milliliter of thrombin²⁰; prothrombin time with activated rabbit brain thromboplastin; and partial thromboplastin time.²¹ Fibrinogen,²² prothrombin (Factor II),²³ accelerator globulin (Factor V),²⁴ anti-hemophilic globulin (Factor VIII)²⁵ and plasma thromboplastin component (Factor IX)²⁶ were assayed in frozen plasma after storage at -80°C.

For the estimation of fibrin split products (FSP) 2-ml samples of blood were collected in glass tubes containing 20 U of kallikrein trypsin inhibitor (Trasylol). When clotting had occurred, 50 U of thrombin (Parke-Davis) were added to each tube. After incubation at 37°C for two hours, serum was obtained by centrifugation at 2000 rpm for 10 minutes. The FSP in this serum were assayed by the method of Claman and Merrill²⁷ except that rabbit antihuman fibrinogen antiserum (Hyland) was employed. FSP were also estimated by the semiquantitative method of Stiehm and Trygstad.²⁸

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Immunofluorescent and Histologic Studies

Tissue samples were snap frozen on dry ice for immunofluorescent study or fixed in 10 per cent formalin for histologic study with hematoxylin eosin, periodic acid-Schiff (PAS) and phosphotungstic acid-hematoxylin (PTAH) stains. Immunofluorescent staining was done with antisera specific for human IgG, IgA, IgM, C3, fibrinogen and equine gamma globulin. The specificity of the antiserum was shown by immunoelectrophoresis and double diffusion in 1 per cent agarose. Immunofluorescent control studies included sections of normal kidney, spleen and liver blocking with unconjugated re-agents and absorption of the reagents with their specific antigens.

Case Reports

Case 1

From January of November, 1969, a 45-year-old multiparous woman on chronic hemodialysis was given an estimated 125 transfusions of A+ blood. Renal homotransplantation was performed on November 28, 1969, from a cadaveric donor of O+ blood type. The recipient serum contained a variety of antidonor antibodies, including lymphocytotoxins, leucoagglutinins and heterohemagglutinins, as well as cytotoxins against the lymphocytes of 99 per cent of random unrelated people. In addition, the preoperative serum was found by Professor Milgrom to have a positive test by the mixed agglutination technic. There were incompatibilities in the antigenic groups HL-A8 and Te6.

Because the rejection of a kidney by a presensitized canine recipient can be ameliorated with a prior graft from the same donor,⁷ it was planned to transplant temporarily a kidney and if necessary a spleen or liver before the definitive renal homograft was placed. Consequently, the donor left kidney, which had a small polar infarct, was removed first and revascularized in the usual way in the recipient right extraperitoneal space. The anticipated immediate rejection did not occur, and the homograft excreted small quantities of bloody urine. Because of the polar infarct, the organ was removed after 80 minutes and replaced with the donor's right kidney. With the 2d kidney diuresis promptly occurred. However, a generalized ooze in the operative wound was now noted. There was evidence of disseminated intravascular coagulation (discussed below), and for that reason a brief course of heparin therapy was tried. Re-exploration for the control of bleeding was necessary 18 hours after transplantation and again after two days. Both times the cortex of the homograft was pink. The transplant became anuric in 5 days, and it was removed after 13 days. The renal artery and vein were open, but the kidney had undergone nearly complete cortical necrosis.

On January 22, 1970, a 7-year-old cadaveric donor of O+ blood type and with histocompatibility mismatches of HL-A groups 2, 3 and 7 became available. One of the kidneys was interposed in the arteriovenous shunt used for hemodialysis. It became pink and made urine for 40 minutes. Its surface then turned mottled and cyanotic as it underwent hyper-acute rejection. There was no clinical evidence of abnormal bleeding at this time or subsequently.

Case 2

A 27-year-old man with end-stage glomerulonephritis was given an estimated 50 blood transfusions in the 6 months before admission to the Denver Veterans Administration Hospital. During this time, he had 3 abdominal operations for duodenal ulcer or intestinal obstruction. Renal homotransplantation was performed from his 24-year-old sister. Both donor and recipient were O+ blood type. The only antigenic mismatch recognized by Dr. Paul Terasaki was of group Te4. No preformed recipient antibodies of the kinds described in Case 1 were detected. At the time of renal transplantation on November 10, 1969, the patient's kidneys, which had been excreting 400 to 600 ml of urine per day, were not disturbed. The homograft

began a diuresis that continued briskly for six hours and then dropped off, so that by 12 hours the urine volume was about the same as it had been before operation (20 to 25 ml per hour). By 36 hours there was total anuria, and the patient had become comatose.

As urine flow diminished there were multiple clinical signs of a serious bleeding diathesis, including hematuria, epistaxis. Subconjunctival hemorrhages, the appearance of blood in the upper gastrointestinal aspirate and hemorrhage from all the skin wounds. Multiple blood cultures were negative. Extensive liver-function tests gave normal results for another day before exhibiting deterioration. After 36 hours, heparin was given intravenously during a 10-hour hemodialysis on a kü artificial kidney. The patient was then returned to the operating room, where all the residual stomach was removed as well as the enlarged spleen. The liver was soft and mottled and was thought to have multiple small necrotic areas. The resected gastric remnant had extensive coagulative mucosal necrosis. Bleeding continued from multiple sites for the remaining 1½ days of life. During this time the right arm and left leg became pulseless. Moreover, several islands of anterior thoracic and abdominal skin became gangrenous. The patient died almost 4 days after revascularization of the renal homograft.

At autopsy, the transplanted kidney was soft and contained multiple perirenal hemorrhages; the renal artery and vein were patent. There was hemorrhage into the lungs, peritoneal cavity and intestines. The esophageal, intestinal and colonic mucosae were friable, with multiple necrotic areas. The liver was studded with multiple yellow infarcts measuring 1 to 30 mm in diameter. The main hepatic artery and its branches were free of thrombosis. Unfortunately, the femoral artery that supplied the lifeless left leg was not dissected. The right brachial artery was filled with a fresh occlusive thrombus.

Results

Immunologic Studies

In the preoperative serum of Case 1, the preponderance of the leukoagglutinins, lymphocytotoxins and heterohemagglutinins were localized in IgG. The antibodies were all absorbed in vitro by the stored hepatic cells of the cadaveric renal donor.

Within a few minutes after revascularization of the first kidney, the antibody titers in samples from the homograft renal vein became less than in systemic blood (Fig. 1). Moreover, the levels of systemic leukoagglutinins and lymphocytotoxins fell perceptibly (Fig. 1). After the first graft was removed and replaced by the contralateral kidney from the same donor, systemic lymphocytotoxins drifted even lower (Fig. 1). Arteriovenous gradients of IgG and IgA developed after the transplantation of both organs (Fig. 1), but this was inexplicably accompanied by sudden increases in the systemic serum concentration of the IgG. When the third homograft was revascularized on the arm shunt, almost two months later, the observations were essentially the same except that antidonor leukoagglutinins were not present in advance of revascularization (Fig. 1).

In Case 2 humoral antibodies were never detectable.

Hematologic and Coagulation Studies

In Case 1 the first renal homograft sequestered leukocytes, platelets, fibrinogen (Factor I) and the Factors II, V and VIII, especially in the first 10 minutes after revascularization (Fig. 2). Since the organ had been cooled by perfusion with 200 ml of cold electrolyte solution that contained 10 mg of heparin, residual heparin that appeared in the renal venous blood contributed to the decrease in Factor V activity.²⁹ However, the other measurements, including Factor I, II and VIII, were not greatly influenced by the heparin.

At the same time as the foregoing intrarenal consumption or shortly afterward, there was prolongation of thrombin, prothrombin and partial thromboplastin times in the blood leaving the homograft (Fig. 2). Although some of these changes were undoubtedly due to residual heparin, much of the antithrombin activity was thermolabile and therefore due to FSP.³⁰ For example, the thrombin time of a 1:1 mixture of the 20-minute plasma with normal plasma was shortened from 110 seconds to 28 seconds if the test plasma was first heated at 60°C for 20 minutes. The FSP also were directly measure by the immunoassay method and revealed striking fibrinolysis (Fig. 2).

During the 80 minutes when the first kidney was vascularized, changes occurred in the systemic blood which were similar to but much less marked (Fig. 3) than those just described in the homograft venous effluent. Subsequently, starting at about that time when the first organ was removed and continuing after the second kidney was transplanted, the abnormalities became profound, with as marked drop of platelets and all clotting factors (Fig. 3). In addition, the euglobulin lysis time became shortened to less than 10 minutes, and large quantities of FSI were detectable (Fig. 3.). These findings of a generalized consumption coagulopathy with fibrinolysis corresponded to the development of a grave bleeding diathesis. About 10 hour after transplantation, systemic heparin (1.3 mg per kilogram of body weight) and epsilon aminocaproic acid (0.1 g per kilogram) were administered. During the next several days the evidence of intravascular clotting and fibrinolysis receded approximately at the same time or shortly before the homograft ceased to function.

The third homograft, which was revascularized on the dialysis shunt eight weeks later, was not flushed with a heparin-containing solution. There was an immediate entrapment of formed blood elements and of all clotting factors within the transplant (Fig. 4). Traces of FSP were detected in the renal venous blood. No notable changes of thrombin, prothrombin and partial thromboplastin times were observed. Except for a transient decrease in the number of arterial platelets, there were no systemic changes.

The coagulation studies in Case 2 were far less complete and are summarized in Figure 5. Within five to 10 hours after revascularization of the homograft the platelets and fibrinogen were reduced to 10 and 45 per cent respectively of their preoperative levels. With the tube precipitin method of Stiehm and Trygstad²⁸ fibrin degradation products accounted for 15 per cent of the column length (normal, less than 0.4 per cent). The prothrombin and partial thromboplastin times were prolonged to 35 and 69 seconds (Fig. 5). The various abnormalities were temporarily improved on the second post-operative day when heparin was given (Fig. 5).

Complete hematologic and clotting studies of systemic blood were obtained in six consecutive patients who recovered without incident after renal transplantation. Appreciable changes were not detected.

Immunofluorescent and Histologic Studies

Since these results were in accord with published observations,^{2,3,5-7,31} attention will be confined to special feature. In Case 1, the first of the three homografts was biopsied at 20, 40 and 80 minutes. The glomerular capillaries of all three specimens contained irregular fibrin deposits. Equivocal deposits of C3 were in patchy distribution along the glomerular basement membrane at 40 minutes, but stainable immunoglobulins were otherwise not identified. The number of polymorphonuclear leukocytes per glomerulus was 30 to 40 at 40 minutes but was reduced by 80 minutes. The second homograft after 13 days had the cortical necrosis, fibrin plugging of vessels and nonspecific immunoglobulin deposition described in an earlier paper.⁵ The third kidney, which was sampled at 2¼, 24, 61, 129 and 146 minutes, had findings similar to those in the first graft except that the C3 was greater and there were patchy traces of IgG and IgM that became less distinct in the later specimens.

The immunofluorescent staining in Case 2 revealed fibrin to be present in the peritubular areas of the homograft and to a lesser extent in the native kidneys which had been affected by immune-complex glomerulonephritis. No fibrin was present in the *glomeruli* of either the native or the transplanted kidneys. A widespread focal deposition of fibrin was present in samples from the splenectomy, and large amounts of fibrin were present in the liver surrounding the necrotic cells of severe mid-lobular necrosis. The hepatic fibrin also stained with the PTAH stain in fibrillar pattern. No specific deposits of IgG, IgA, IgM, C3 or equine gamma globulin were seen in the renal homograft or the native spleen or liver.

Discussion

The emphasis that has been placed in this report on coagulation changes has not been intended to minimize the etiologic role of immunologic factors in abrupt renal rejection. It has been accepted that hyperacute renal rejection is the reflection of sensitization to antigens found in the donor^{1-5,7,32} although it has also been pointed out⁵ that antidonor antibodies apparently can be present despite good histocompatibility match and that none of the current serologic methods can predict the sensitized state with total reliability. One of the recipients of the present study had preformed antibodies detectable by four different procedures, whereas the same examinations were negative in the other patient. Yet similar changes in coagulation consequent to homotransplantation swiftly evolved in the systemic blood of both the recipients. Such changes were not seen in six other patients who had benign convalescence after renal transplantation.

The observations in the two patients of the present report were analogous to those reported by Simpson et al.,⁷ who sensitized dogs by repeated skin grafts and subsequently transplanted the liver, spleen or kidney from the same donor. The canine organs promptly sequestered antigraft humoral antibodies, platelets, white cells and clotting factors. Moreover, the graft venous effluent contained fibrinolytic activity. In about a fourth of the dogs a systemic coagulation disorder then developed, with abnormalities often associated with disseminated intravascular coagulation.³³⁻³⁵

Similar trapping of antibodies, formed blood elements and clotting factors was documented in Case 1 after the transplantation of consecutive grafts from the same donor. Nevertheless, these kidneys were not destroyed immediately, possibly because the fibrinolysis that quickly developed had a protective effect. The findings in sequential renal-graft biopsies were consistent with this interpretation, with an initial laying down and later removal of fibrin in the vascular system. At the same time, there was first entrapment and then release by the homograft of both platelets and white cells. Conceivably, factors that contributed to the life-threatening systemic coagulopathy originated from the transplant as well. In the other less completely studied patient (Case 2), eventually lethal changes occurred within five hours that were diagnostic of disseminated intravascular coagulation with consumption of clotting factors, fibrinolysis and a clinical bleeding diathesis.

Further comment is appropriate about the variability with which alterations in coagulation may become manifest in a given recipient. In Case 1, whose first two renal homografts provoked a life-threatening bleeding diathesis, a child cadaveric kidney was later inserted into the arteriovenous shunt used for dialysis. There was immediate consumption of antibodies, white cells, platelets and clotting factors within the graft, which became cyanotic in less than an hour. Hyperacute rejection apparently occurred so rapidly on this occasion that secondary events such as systemic fibrinolysis or other generalized clotting alterations did not have time to develop before the transplanted kidney was functionally excluded from the circulation by its devascularization. Thus, the outcome in terms of both graft survival and host peril presumably depends on many factors discussed at length previously⁵ including the kind and intensity of

the initiating immunologic reaction, as well as the balance of coagulation and fibrinolysis with which the host responds. The observations of Braun and Merrill³¹ and Busch et al³⁶ are consistent with this interpretation.

In principle, the chain of events in this kind of homograft rejection is not obviously different from that seen after the heterotransplantation of organs between animals of genetically diverse species.³⁷ With the hyperacute rejection of both homografts and heterografts, the means of inducing a local or generalized coagulopathy have not been identified although likely mechanisms are not difficult to envision. Since the preformed antibodies appear to react with antigens in the transplants, clotting could be induced directly by the antibody-antigen reaction^{38–40} or by the consequent tissue injury. In addition, antibody-antigen reactions attract polymorphonuclear leukocytes via C' activation,⁴¹ and these white cells appear capable of inducing clotting⁴² and are an important if not essential intermediary in the causation of the thrombosis seen in the local⁴³ and generalized⁴² Schwartzman reactions. Heavy accumulations of polymorphonuclear leukocytes and thrombosis have been seen in man, in whom preformed antibodies induced immediate hyperacute rejections of renal transplants.^{3,5,44} In Case 1 of the present report, white cells were promptly sequestered by the homograft as shown by noteworthy arteriovenous gradients. The polymorphonuclear leukocytes were obvious in the sequential biopsies within 40 minutes and then apparently began to leave the grafts.

In a past publication⁵ the possibility was discussed that a coagulopathy (and consequent hyperacute rejection) could be precipitated by an antigen-antibody reaction outside, as well as within, a renal graft. If the immunologic reaction occurred at a distance from the homograft, the transplanted kidney could conceivably be destroyed as an “innocent bystander” by becoming the passive repository of fibrin products that are formed elsewhere and filtered out by the renal microcirculation. From the animal experiments carried out by Simpson et al.⁷ and from the further observation in the human patients herein reported, it seems clear that the antigen-antibody reaction that triggers the coagulation probably is nearly always within the transplanted organ, that the coagulation changes often are confined to the transplant, and that if systemic coagulation abnormalities develop, these are derivative from events within the homograft. Under these circumstances, a systemic coagulation disorder initiated in the kidney and then secondarily occurring elsewhere could be conceived as having a boomerang effect in which the fibrin strands from distant intravascular coagulation could be circulated back to a homograft and contribute to its further injury.

Various descriptive terms have been applied to hyperacute rejection, and its different aspects have been emphasized by comparison to the Arthus reaction,⁴⁴ inverse anaphylaxis³ and the generalized Schwartzman reaction.³ Each of these classic immunologic phenomena is, or can be initiated by interaction of antibody and antigen. After the immunologic reaction in each of these, there are multiple secondary events, including inflammation and coagulation. The importance of the coagulation varies in the different phenomena, being the central event in the generalized Schwartzman reaction. However, since all these classic terms have additional connotations that may not apply directly to hyperacute rejection, it is probably preferable simply to define this kind of rejection as an “immunologically mediated coagulopathy that may lead to the devascularization and destruction of a transplanted organ and that sometimes results in the coagulation abnormalities.”

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Abbreviations

ALG	antilymphocyte globulin
DEAE	diethylaminoethanol
FSP	fibrin split products
PTAH	phosphotungstic acid hematoxylin

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Figure 1.

Antibodies and Immunoglobulin Concentrations in Systemic Blood (Solid Lines) and in Samples from the Renal Veins Draining the Homografts (Dashed Lines) in Case 1.

The first two kidneys were consecutively transplanted in the right iliac fossa after removal from the same cadaveric donor. The final kidney was revascularized extracorporeally.

Figure 2.

Intraoperative Coagulation Studies in systemic Blood (Solid Lines) and in Venous Blood Returning from the Homograft (Dashed Lines) in Case 1 (First Homograft).

Note the consumption of platelets and clotting factors and the evidence of fibrinolytic activity in the venous effluent (see text). FSP are measured quantitatively.

Figure 3.

Profound and Lasting Systemic Coagulation Changes in Case 1 Produced by the Consecutive Transplantation of Two kidneys (I and II) from the Same Donor.

Note that the data are an extension of the more detailed studies presented in Figure 2 and that the time between transplantation of the first and second kidneys is 80 minutes. EACA indicates epsilon aminocaproic acid. The two operations were for control of wound hemorrhage.

Figure 4.
Extracorporeal Transplantation of a Child Donor's Kidney in Case1.
Hematologic and coagulation changes occurred in renal arterial (solid lines) and renal venous (dashed lines) blood. Note the local consumption but no detectable systemic effect.

Figure 5.

Urinary Output, Immunosuppressive Treatment and Coagulation Studies in a 27-Year-Old Recipient Whose Renal Homograft Underwent a Violent Early Rejection.

A disseminated intravascular coagulation, fibrinolysis and a bleeding diathesis developed. FSP were measured with a semiquantitative analysis.²⁸