

HYPERACUTE REJECTION OF A FIRST KIDNEY ALLOGRAFT ASSOCIATED WITH PRE-EXISTING HUMORAL ANTIBODIES AGAINST DONOR CELLS

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This paper deals with a human kidney transplant that failed to function from the moment of revascularization, in the absence of any technical difficulty. This case is described and discussed together with the data of similar cases found in the literature.

Our patient was a 24-year-old white male who since the age of 10 had been suffering from frequent throat infections and bronchial asthma. At the age of 12 years, nephropathy was diagnosed for the first time, and this gradually led to renal insufficiency.

In 1966, a kidney biopsy showed numerous hyalinized glomeruli with dense, thickened capsules. At the same time he had a creatinine clearance of 4.6 ml/min. and negative urine cultures. Since the summer of 1967 and because of the severe renal insufficiency he was submitted to periodic dialysis. A kidney graft was recommended in the autumn of the same year.

In the course of the disease this patient received a total of 20 transfusions, mostly of packed red cells, which were generally followed by intense allergic reactions with urticaria and papulae responding well to the administration of antihistaminics.

The only prospective donor was his 52-year-old mother. She suffered from bronchial asthma and cholelithiasis, but had normal kidney function.

Histocompatibility typing was done on the mother's and the patient's cells, by sending blood to Los Angeles. With the lymphocyte cytotoxicity test (Terasaki *et al.*, 1968), the recipient was positive for groups 1 and 6, whereas the donor was positive for group 6 only, showing no major group incompatibility. Thus, when analyzed for seven major groups, no incompatibility could be shown and only a minor mismatch by consideration of each individual's serum.

A cross-matching test in which the donor's cells were tested with the recipient's serum was, however, very strongly positive in all three dilutions tested. The fact that the recipient was presensitized, and had circulating antibodies, was further confirmed by testing his serum with lymphocytes from 30 random donors. Cells from 6 of these individuals were damaged. The conclusion is that, although the compatibility as far as the seven major known groups was good, the recipient possessed preformed antibodies to other antigen(s) of the mother, and matching grade F was assigned.

Because the antibody was not directed against a recognized major group and because the mother was the only available donor, the transplant was performed in October 1967.

On revascularization, the kidney assumed a normal colour, but did not start producing urine. After 24 hours without urine output, the patient was reoperated. The kidney appeared cyanotic and the ureter was flaccid, the distal part being apparently necrosed. A new bladder anastomosis was made, but no urine was secreted. A renal biopsy produced little haemorrhage.

On microscopic examination (Fig. 1), the parenchyma appeared weakly stained due to necrosis, the small vessels were thrombosed in various zones. No cellular infiltration was observed.

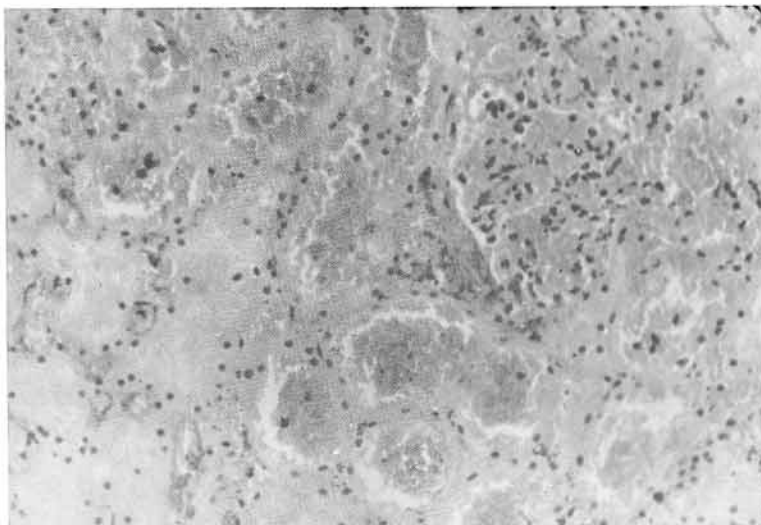


Fig. 1

Figure 2 shows a higher magnification. This microscopic picture corresponds to that described in other instances of immediate 'rejection'.

Eleven days after grafting the patient was reoperated. The kidney appeared pale, soft and did not bleed when a biopsy was taken. On microscopic examination it showed complete diffuse necrosis.

Fifteen days after grafting the kidney was removed (Fig. 3). An arteriography of the graft, after removal, showed obstruction of the small and medium arteries.

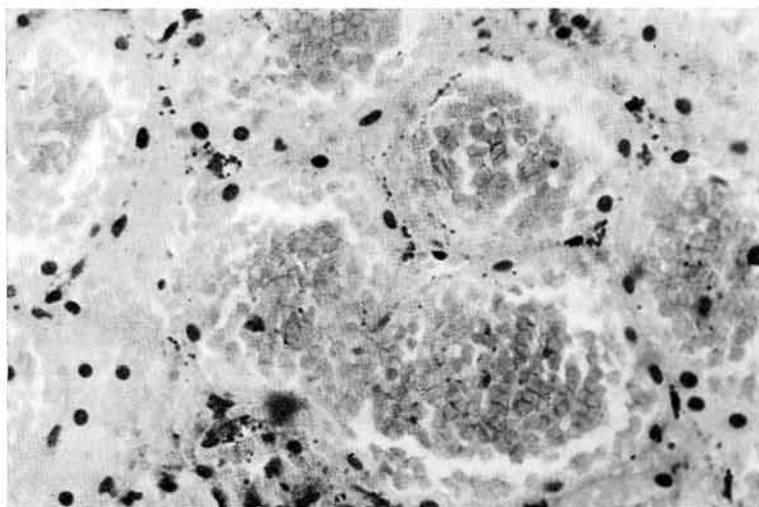


Fig. 2

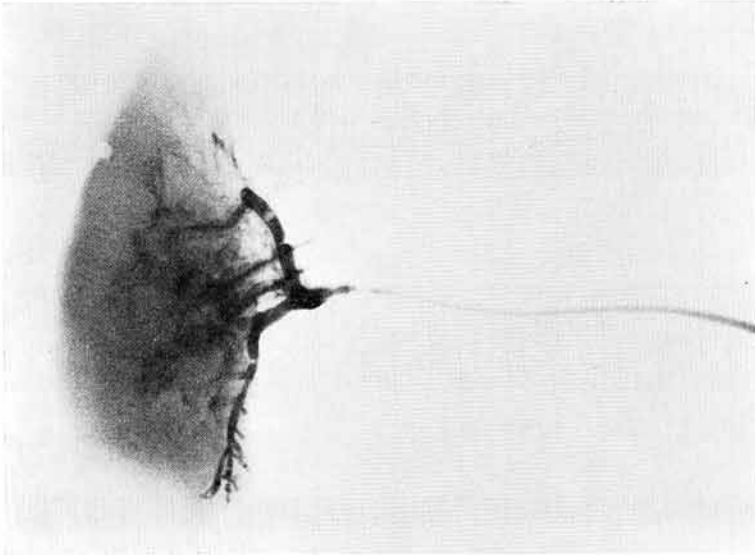


Fig. 3

A second radiograph (Fig. 4) taken a moment later, when the contrast substance was already leaving the kidney through the vein, indicated that the entire cortical area remained non-vascularized.

The patient was maintained on periodic dialysis but died of generalized sepsis, 32 days after grafting.

In view of the previous transfusions and of the pre-existing antibodies to the donor cells, it is tempting to postulate a hyperacute tissue transplantation rejection. However, it is our feeling that the mechanism of this type of kidney failure is by no means clear.

On reviewing the literature we find a number of immediate failures in kidneys otherwise transplanted with no technical difficulty. Some of these grafts are seen to become cyanotic as soon as vascularization is re-established.

Porter in 1965 described this sort of situation in kidney grafts incompatible for the ABO red blood cell groups.

Kissmeyer-Nielsen *et al.* (1966) described two cases of hyperacute rejection of human kidney allografts in the presence of pre-existing humoral antibodies against donor cells.

Terasaki *et al.* (1967) discussed the data of 7 cases of 'immediate kidney transplantation rejection' occurring in various institutions.

More recently, Starzl *et al.* (1968) observed immediate transplantation failure in five grafts carried out in three patients, all in the course of 6 weeks. It must be pointed out that in these kidneys Starzl *et al.* (1968), using immunofluorescence methods, demonstrated that there was no immunoglobulin present, or else there was so little that it could be considered non-specific trapping rather than the result of a sustained immunological reaction.

We believe the type of reaction we are talking about can be clearly separated from the acute rejection crisis appearing in the first weeks after grafting. It may be defined by the following characteristics: (a) sudden and irreversible termination of the renal function; (b) lack of response to immunosuppressive therapy and to immediate high dose steroid therapy; (c) a microscopic picture consisting of: thrombosis of the small vessels, diffuse parenchymal necrosis, and absence of cellular infiltration.

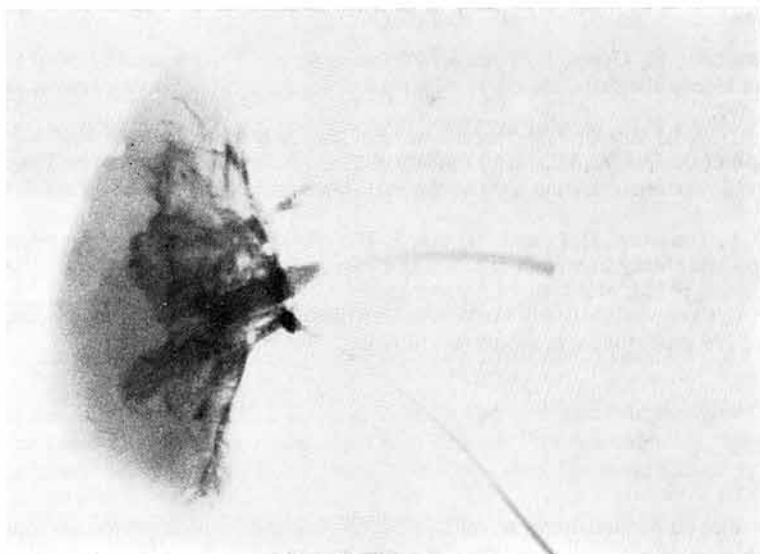


Fig. 4

So far, this picture has been observed in three different immunological situations:

1. Kidney grafts incompatible for the ABO red blood cell antigens, in which one may assume pre-existing 'natural' antibodies for the ABO-incompatible antigens.
2. Kidney grafts compatible for the ABO system but with circulating antibodies in the recipient reacting with donor cells *in vitro*.
3. Kidney grafts with no pre-existing demonstrable antibodies in the recipient.

On the other hand, Terasaki has observed two grafts in which, in spite of the existence in the receptor of circulating antibodies against the cells of the donor, this type of reaction did not occur. Obviously, the existence of circulating antibodies is not sufficient. It may be necessary for the recipient to have some peculiar allergic background (our patient had a history of asthma and urticarial reactions to transfusions). Or else, it may be necessary that the antibodies be of a certain type.

Some of the above-mentioned authors have speculated on the possibility that in all these cases we may be dealing with a Schwartzman-Sanarelli type of reaction, the kidney failure being the end result of an acute intravascular antigen-antibody reaction with subsequent local thrombosis and ischaemia. The antigens involved in these reactions could well be in some instances donor cells or tissue antigens, perhaps released to the vascular cavity during the period of ischaemia. In other cases, the sensitizing antigens could come, as suggested by Starzl *et al.* (1968), from previous infections or from bacterial contaminants in the solutions used in previous dialysis.

It is interesting to note that intravascular haemolysis, the use of azathioprine and of steroids tend to diminish the capacity of the reticuloendothelial system, and that the Schwartzman-Sanarelli phenomena are enhanced when this system is partially blocked.

Should the proposed mechanism for these hyperacute reactions prove correct, this would have some practical implications. First of all these graft failures should not be treated with increased doses of azathioprine or steroids. Instead, heparin and fibrinolytic agents should be given immediately. Also, it would be justified to recommend systematic addition of anti-histaminic and fibrinolytic agents to the fluid used for the perfusion of the kidney before transplantation as a preventive measure for this kind of accident.

REFERENCES

- KISSMEYER-NIELSEN, F., OLSEN, S., POSBORG PETERSEN, V. and FJELDBORG, O. (1966): Hyperacute rejection of kidney allografts, associated with pre-existing humoral antibodies against donor cells. *Lancet*, 2, 662.
- PORTER, K. A. (1965): Morphological aspects of renal homograft rejection. *Brit. med. Bull.*, 21, 171.
- STARZL, T. E., LERNER, R. A., DIXON, F. J., GROTH, C. G., BRETTSCHEIDER, L. and TERASAKI, P. I. (1968): The Shwartzman reaction after human renal homotransplantation. *New Engl. J. Med.*, 278, 642.
- TERASAKI, P. I., THRASHER, D. L. and HAUBER, T. H. (1968): Serotyping for homotransplantation. XIII. Immediate kidney transplant rejection and associated preformed antibodies. In: *Advance in Transplantation*, p. 225. Munksgaard, Copenhagen.
- TERASAKI, P. I., VREDEVOE, D. L. and MICKEY, M. R. (1967): Serotyping for homotransplantation. X. Survival of 196 grafted kidneys subsequent to typing. *Transplantation*, 5, 1057.