

type of graft under investigation. Combined treatments with other immunosuppressive agents are now under investigation in our laboratory.

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LITERATURE CITED

1. Liacopoulos M, Lambert F, Liacopoulos P: 1980 *Immunology* 41: 143

2. Hilyert I, Horejsi V, Angelisova P, et al: 1980 *Nature* 284: 273
3. Weil R III, Nozawa M, Chermack W, et al: 1974 *Transplantation* 17: 600
4. Laux DC, Davignon DJ: 1980 *Cell Immunol* 50: 202
5. Howard IK, Sage HJ, Stein MD, et al: 1971 *J Biol Chem* 246: 1590
6. Howard IK, Sage HJ: 1969 *Biochemistry* 8: 2436
7. Studier FW: 1973 *J Mol Biol* 79: 237
8. Fliegerova O, Salvetova A, Ticha M, et al: 1974 *Biochim Biophys Acta* 351: 416
9. Nelken D, Friedman EA, Morse SI, et al: 1977 *Transplant Proc* 9: 333

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HYPERACUTE REJECTION OF A TRANSPLANTED HUMAN HEART¹

The possibility of hyperacute rejection has not generally been considered an important concern in human cardiac transplantation. Cardiac replacement is often carried out under time constraints which make histocompatibility testing impractical. The donor heart may be harvested hundreds of miles away from the recipient, and the limited period of safe cardiac preservation then argues against taking time for direct lymphocyte crossmatching of donor with recipient before the transplant operation is done (1).

A patient is reported in whom hyperacute cardiac rejection occurred on the operating table. The direct lymphocyte crossmatch test, which was not completed preoperatively, subsequently showed that the recipient had performed cytotoxic antibodies which reacted strongly against donor lymphocytes.

A 56-year-old woman developed cardiogenic shock following recurrent myocardial infarction. She initially required intra-aortic balloon support, transvenous pacemaker, and vasopressors for survival. Although gradual withdrawal of some of these support measures was possible, she nevertheless remained hemodynamically unstable and bedridden with intractable congestive heart failure. Cardiac catheterization revealed severe left ventricular dysfunction with ejection fraction of less than 20% of predicted normal. Coronary angiography demonstrated three vessel disease with distal involvement not amenable to coronary artery bypass. The referring cardiologist requested urgent cardiac transplantation as the only possible way of saving the patient.

A young ABO compatible brain-dead donor became available almost immediately, and heart replacement was carried out using a surgical technique of Shumway (2). The donor heart was preserved by perfusion with cold cardioplegia solution (3). Total ischemia time was 70 min. Spontaneous donor heart beat began very quickly after removal of the aortic cross clamp. No technical problems with any of the anastomoses or with trapped air were evident as total bypass was discontinued.

Approximately 15 min after partial cardiopulmonary bypass was established, the heart suddenly became asystolic, mottled, and cyanotic. Total cardiopulmonary bypass was reinstated and atrial ventricular sequential pacing was started via epicardial atrial and ventricular wires. Isuprel and epinephrine were

administered and 1 g of methylprednisolone was given i.v. These temporarily improved cardiac function and cardiopulmonary bypass was discontinued with the heart beating in normal sinus rhythm. Three additional bolus doses of 1 g of methylprednisolone were given. At the conclusion of the operation, cardiac output again fell and a dopamine drip was started. Approximately 2 hr later, an intra-aortic balloon was inserted because of persistently low cardiac output. The patient died in intractable cardiogenic shock approximately 4 hr after operation.

A direct crossmatch between the patient's serum and the donor's lymphocytes, done at room temperature without separation of donor cells into B and T lymphocytes, revealed 100% killing of donor cells by the recipient's serum. This test was not completed until after the heart transplant was finished. Subsequent postmortem lymphocytotoxicity testing of the recipient's serum was done to better characterize the recipient antibodies.

B and T lymphocytes were isolated by nylon-wool column and tested using the standard lymphocyte microtoxicity test (4). When the pretransplant serum was tested against a panel of T and B lymphocytes at different temperatures, 33% of the panel of T lymphocytes was completely killed by the serum. The power of these kill reactions strongly suggests that the patient had antibodies to T lymphocytes. The test panel consisted of lymphocytes from 24 normal patients. When tested against B lymphocytes, the pretransplant serum reacted with 42% of the panel at 37 C and 25% of the B cell panel at 5 C. Thus, both the T cell and B cell reactivity was mostly produced by warm-reactive antibodies. In order to determine whether the antibodies might be against HLA-DR or ABC, the serum was absorbed with pooled platelets. All of the reactivity was removed by platelets, indicating that the antibodies were against HLA-ABC antigens.

At autopsy, microscopy of the donor heart revealed diffuse interstitial edema and some focal hemorrhage. Small arteries, arterioles, capillaries, and venules were extensively plugged by platelet aggregates. There were also some intravascular fibrin and sludged red blood cells. Marginating neutrophil polymorphonuclear leukocytes were also present within the capillaries and venules. Some capillaries were disrupted. Mononuclear cells were rare. These microscopic findings were interpreted as hyperacute rejection.

Acute rejection of heart transplants, mediated primarily by

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T lymphocytes, has been observed on many occasions in animals and in humans (2, 5-11). Hyperacute heart rejection mediated by preformed cytotoxic antibody has been described in cross species heart transplantation (12) and in cardiac allografts in dogs (13) and rats (14), when the recipients had been presensitized. Up to now it has not been reported in human heart transplants.

In this case the patient's very unstable blood pressure, combined with our perception that hyperacute rejection was a very unlikely possibility, led us to proceed with heart replacement without waiting for the results of the direct crossmatch test. The patient's cardiogenic shock was so resistant to treatment that she almost certainly could not have survived long enough to wait for a crossmatch-negative heart donor, even if the results of the crossmatch with the actual donor had been known before transplantation. However, the predictive value of the crossmatch test is evident in this case and represents an observation which is clinically important for heart transplant recipients who are hemodynamically stable enough to wait for a crossmatch-negative donor.

At the time of the original crossmatch, the serum was not tested against B and T lymphocytes. There are indications that a crossmatch reactive against B lymphocytes does not result in a hyperacute rejection in kidney transplants (15). In this instance, it was not possible to retrospectively determine whether the positive crossmatch obtained was against T or B cells. However, the fact that all of the donor cells were killed by the patient's serum indicates that a T cell-positive crossmatch had been obtained. Subsequent tests with B and T cell panels also suggest that this indeed was a positive T cell crossmatch. The patient had antibodies to both T and B cells, but since this activity could all be removed by platelets, it is likely that HLA-ABC antibodies were involved and not HLA-DR antibodies.

Although there was not so much interstitial hemorrhage in the transplanted heart as has been described in cardiac allografts in presensitized dogs (13) and rats (14), the microscopic findings are entirely consistent with the clinical diagnosis of hyperacute rejection.

This report documents hyperacute rejection of a transplanted human heart in association with a positive direct cytotoxic crossmatch between the patient's serum and the donor's lymphocytes. The probability of hyperacute heart rejection in the presence of a positive crossmatch cannot be estimated from this case or from the reported experience from other centers, which includes two transplants done in the presence of a known positive crossmatch at Palo Alto (2) and at Madison (16), in which hyperacute rejection did not occur. Nevertheless, because of the possibility of hyperacute rejection, cardiac transplantation should not be done in the face of a positive anti-T cell donor crossmatch, unless the patient is not expected to survive long enough to wait for another donor.

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LITERATURE CITED

1. Watson DC, Reitz BA, Baumgartner WA, et al. Distant heart procurement for transplantation. *Surgery* 1979; 86: 56.
2. Baumgartner WA, Reitz BA, Oyer PE, Stinson EB, Shumway NE. Cardiac homotransplantation. *Curr Probl Surg* 1979; 16: 1.
3. Braimbridge MV, Chayen J, Bitensky L, Hearse DJ, Jynge P, Cankovic-Darracott S. Cold cardioplegia or continuous coronary perfusion? Report on preliminary clinical experience as assessed cytochemically. *J Thorac Cardiovasc Surg* 1977; 79: 900.
4. Terasaki PI, Bernoco D, Park MS, Ozturk G, Iwaki Y. Microdroplet testing for HLA-A, -B, -C, and -D Antigens. *Am J Clin Pathol* 1978; 69: 103.
5. Barnard CN. Human heart transplantation. The diagnosis of rejection. *Am J Cardiol* 1968; 22: 811.
6. Ellis B, Madge G, Kolhatkar M, Still W. Clinical and pathological findings in human cardiac rejection. *Arch Pathol* 1971; 92: 58.
7. Griep RB, Stinson EB, Dong E Jr, Clark DA, Shumway NE. Acute rejection of the allografted human heart. *Ann Thorac Surg* 1971; 12: 113.
8. Lower RR. Rejection of the transplanted heart. *Transplant Proc* 1969; 1: 733.
9. Nora JJ, Cooley DA, Fornbach DJ, et al. Rejection of the transplanted human heart. *N Engl J Med* 1969; 280: 1079.
10. Rapaport FT, Dausset J. Immunological principles of donor selection for human cardiac transplantation. *Prog Cardiovasc Dis* 1969; 12: 119.
11. Williams GM, Deplanque B, Graham WH, Lower RR. Participation of antibodies in acute cardiac allograft rejection in man. *N Engl J Med* 1969; 281: 1145.
12. Weil R, III, Nozawa M, Weber C, et al. Cardiac heterotransplantation. *Transplantation* 1975; 19: 150.
13. Sharma HM, Rosensweig J, Chatterjee S, Moore S, de Champlain M-L. Platelets in hyperacute rejection of heterotopic cardiac allografts in presensitized dogs. *Am J Pathol* 1973; 70: 155.
14. Forbes RDC, Kuramochi T, Guttman RD, Klassen J, Knaack J. A controlled sequential morphologic study of hyperacute cardiac allograft rejection in the rat. *Lab Invest* 1975; 33: 280.
15. Ettinger RB, Terasaki PI, Opelz G. Successful renal allograft across a positive cross-match for donor B-lymphocyte alloantigens. *Lancet* 1976; 2: 56.
16. Kahn DR, Hong R, Greenberg AJ, Dacumos GC, Dufek JH. Total lymphoid irradiation and donor bone marrow for human heart transplantation. Abstracts of Eighth International Congress of the Transplantation Society (July) 1980; F11.2.

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