

## AUTOPSY FINDINGS IN A LONG-SURVIVING LIVER RECIPIENT

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IT has been a little more than five years since the first extended survival was achieved after human liver transplantation, and for that reason individual cases are still of special interest. For a long time, the longest survivor after such a procedure was a child in whom the indication for operation had been biliary atresia. After almost 3½ years of good health, the patient died after an acute illness. The last events of his life and the autopsy findings are the principal subjects of this report.

### CASE REPORT

Orthotopic liver transplantation was performed at the Colorado General Hospital on July 20, 1968, as reported elsewhere under the code designation of OT 19.<sup>1</sup> The Caucasian male recipient was 4 years old and was given a homograft from a 10-year-old cadaveric Negro male donor. The direction of blood groups was O to B. There were incompatibilities of HL-A 2, 3 and 7 (E Terasaki match).

Throughout most of his subsequent life, immunosuppressive treatment was with azathioprine, prednisone and horse antilymphocyte globulin. There were easily reversed rejection episodes after 1 and 2 months during which the highest bilirubin increases were to 6.1 mg per 100 ml. Except for low-grade and persistent transaminase increases (50 to 200 IU, normal <50), the patient subsequently had essentially normal liver function at all times after transplantation until the final hospital admission. Because of these transaminase elevations, cyclophosphamide was substituted for azathioprine in June, 1971. His general health was excellent except for a bout of chicken pox in November, 1969 (16 months after transplantation), which was treated at the University of Minnesota Hospital with convalescent plasma. Immunosuppressive therapy during the last year of outpatient life was 25 mg per day of azathioprine (or cyclophosphamide), 15 to 20 mg per day of prednisone and 1 injection per week of horse antilymphocyte globulin. In the 3½ years of survival, his height increased from 96 to 100 cm, and his weight from 14.3 to 27.2 kg.

On October 27, 1971, the patient was admitted to the University of Minnesota Hospital with acute septicemia (*Haemophilus influenzae*, Type B) of less than 1 day's duration, complicated by circulatory collapse, evidence of disseminated intravascular coagulation and acute deterioration of both renal (rise in blood urea nitrogen to a maximum of 113 mg per 100 ml) and hepatic function. The SGOT was increased for 8 days, reaching a zenith of 7700 IU on the 3d day. The bilirubin rose from normal to a peak of 21.9 mg per 100 ml. Alkaline phosphatase rises did not occur at that time but developed 10 days later. Prothrombin levels were acutely depressed to 25 per cent with recovery over the next week. Initially, all immunosuppressive thera-

py was stopped, but subsequently, because of the fear that rejection was contributing to the deteriorated hepatic function, treatment with azathioprine and antilymphocyte globulin was resumed along with variable increases of the prednisone dose to as high as 100 mg per day. The bilirubin remained at 15 to 20 mg per 100 ml. Eventually, the alkaline phosphatase became persistently elevated, and the prothrombin time returned to normal. At the same time, renal function returned to normal. In late November, extensive vesicular lesions of the right leg developed from which varicella-zoster virus was cultured. The patient's condition deteriorated, with diffuse pneumonitis that required ventilator support. He died of respiratory distress on December 9, 1971, 3 years, 4 months and 20 days after the original transplantation.

At autopsy, extensive pneumonitis was found due to *Pneumocystis carinii* and cytomegalovirus. In addition, typical branching hyphae of aspergillus were identified in small scattered pulmonary abscesses. The small branches of the pulmonary arteries contained organizing thrombi. The kidney and brain cells as well as the lungs and hepatic homograft contained inclusion bodies typical of cytomegalovirus, and from the latter two organs, positive cytomegalovirus cultures were obtained. Incidentally, cytomegalovirus had been regularly cultured from the patient's urine, blood and throat for the preceding 3 years. An adenovirus Type II was also isolated from the lungs and the graft at autopsy. The thymus was grossly atrophic, and microscopically there were scattered epithelial islands; the cortex was thinned and contained scattered small lymphocytes. The lymph nodes contained very few lymphocytes, no lymphoid follicles and no germinal centers. The bone marrow was grossly normal.

The liver was green, and had a nodular surface. It weighed 541 g, as compared to a predicted value of 594 g based on 2.2 per cent of total body weight. A post-mortem cholangiogram showed an essentially normal extrahepatic duct system, with well visualized intrahepatic ramifications. The duct reconstruction had been with cholecystoduodenostomy.

It was possible to compare the histologic findings with those of an open biopsy 9 months earlier. In the autopsy specimen there was almost complete occlusion of most of the small hepatic-artery branches and arterioles by massive intimal thickening (Fig. 1), in spite of which a post-mortem angiogram showed the arterial system to be open throughout the graft. However, a number of the vessels in the arteriogram appeared to be narrowed (Fig. 2).

There was marked atrophy of the centrilobular hepatocytes in all lobules, and small focal areas of necrosis of liver cells were present in some of the lobules. Cholestasis was marked, with intracanalicular bile thrombi in the central parts of the lobules. The walls of the central veins were thickened, and there was condensation of the centrilobular reticulum. The larger hepatic veins had no phlebosclerosis, and these had free drainage into the vena cava and through the upper venous anastomosis. The portal tracts contained increased amounts of connective tissue, and a few fine septa extended into some of the lobules, but there were no regeneration nodules, nor was there cellular infiltration.

The gallbladder mucosa was ulcerated, and the submucosa fibrous. Some nuclei in the damaged wall showed cytomegalovirus-like inclusions.

In the open biopsy 9 months earlier, several of the hepatic-artery branches had been narrowed by intimal thickening, but many others had been normal. Fibrosis had been confined to the portal tracts; the hepatocytes had been normal, with no cholestasis.

### DISCUSSION

It is almost certain that the sudden late deterioration of homograft function was a complication of the hemophilus septicemia. Both the native kidneys and the liver homograft were seriously damaged by this incident. The kidney injury reversed relatively completely, but the liver did not recover.

The subsequent loss of the patient was particularly disheartening in view of the very stable function during the preceding 3 years. This outcome was unquestionably due to the effective immunosuppression,

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Figure 1. Human Liver Allograft 3½ Years after Transplantation (Weigert's Elastic Stain X70 before Reproduction).

A branch of the hepatic artery is greatly narrowed by intimal thickening. There is negligible cellular infiltration.

which, in turn, was reflected morphologically by the striking depletion of the lymphoid tissues.

Of course, this immunosuppression provided the background for all the ultimate infectious problems. The continuous susceptibility to infections was illus-

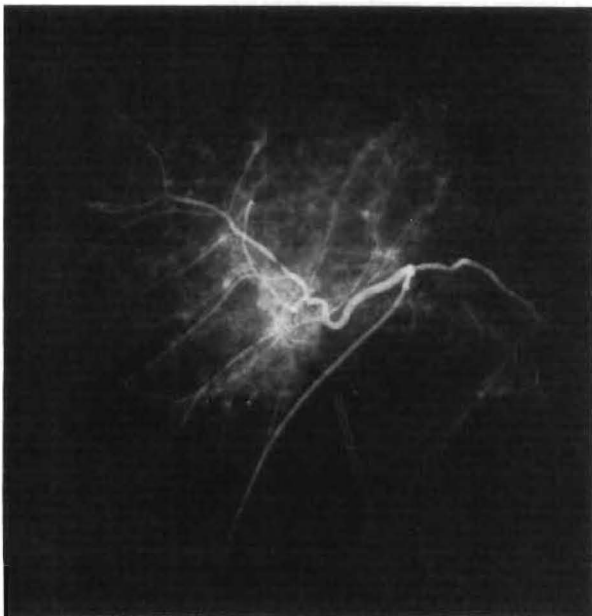


Figure 2. Hepatic Arteriogram Taken at Autopsy.

Note that main vessels are patent, but that several constrictions are present, presumably owing to the lesions shown in Figure 1.

trated in many ways, of which one was the repeated demonstration of cytomegalovirus infestation that at autopsy was confirmed by the finding of cytomegalovirus in multiple organs.

In spite of this continuous immunosuppression, the graft was not normal and had undergone morphologic deterioration even in the last nine months of life. The most dramatic abnormalities were in the vascular system, as has previously been reported in renal,<sup>2</sup> hepatic<sup>3</sup> and cardiac grafts.<sup>4</sup> The ultimate prognosis of these hepatic arterial changes would undoubtedly have been adverse even though post-mortem angiography showed the larger vessels to have adequate lumens. Other altered features consisted for the most part of early fibrosis of the kind previously well documented long after both canine and human homotransplantation.<sup>3</sup>

The frequency with which vascular changes have been found in all kinds of whole-organ homografts had made this finding the central morphologic feature of "chronic rejection." There have been recent advances in the understanding of this apparently immunologic complication. It seems most probable that the vascular lesions are the result of either an antigen-antibody reaction in the vessel walls or the deposition of immune complexes at this site although direct support for this pathogenesis was not provided by immunofluorescence examination of the graft. A very close association has been noted between the appearance of humoral antibodies in patients with renal homografts and the occurrence of vascular lesions in the transplant.<sup>5</sup> There is also increased complement uptake by renal and hepatic grafts<sup>6,7</sup> and the antibody-induced accumulation of platelets<sup>8</sup> and fibrin<sup>9</sup> at this site in late rejection episodes. The mixture apparently becomes covered with a new layer of endothelium, is incorporated into the vessel wall, and with repair leads to narrowing or even obliteration of the arteriolar and arterial lumens. Support for this hypothesis comes from animal experiments in which brief exposure of segments of arterial wall to alloantibody *in vivo* is followed by localized intimal thickening.<sup>10</sup>

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