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Liver replacement for alpha$_1$-antitrypsin deficiency

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A 16-year-old girl with advanced cirrhosis and severe alpha$_1$-antitrypsin deficiency of the homozygous Pi^{ZZ} phenotype was treated by orthotopic liver transplantation. After replacement of the liver with a homograft from a donor with the normal Pi^{MM} phenotype, the alpha$_1$-antitrypsin concentration in the recipient's serum rose to normal; it had the Pi^{MM} phenotype. Two and a third years later, chronic rejection necessitated retransplantation. Insertion of a homograft from a heterozygous Pi^{MZ} donor was followed by the identification of that phenotype in the recipient's serum. Neither liver graft developed the alpha$_1$-antitrypsin glycoprotein deposits seen with the deficiency state. These observations confirm that this hepatic-based inborn error of metabolism is metabolically cured by liver replacement.

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ALPHA$_1$-ANTITRYPSIN, an inhibitor of proteolytic enzymes such as trypsin, chymotrypsin, and collagenase, is the major alpha$_1$-globulin of human plasma. Hereditary alpha$_1$-antitrypsin deficiency, homozygous phenotype ZZ, predisposes to congenital infantile cirrhosis[18] and, occasionally, adult cirrhosis,[22] pulmonary emphysema of early onset in adults,[11] and, rarely, both hepatic and pulmonary disease in childhood[8] or adult life.[7]

Two and a half years ago, we carried out liver replacement in a 16-year-old patient with severe cirrhosis caused by alpha$_1$-antitrypsin deficiency, Pi^{ZZ} phenotype. Following the operation the alpha$_1$-antitrypsin phenotype and concentration reverted to normal. When the graft was rejected and retransplantation was performed 2$^1/_3$ years later, the recipient again adopted the donor phenotype, this time the heterozygous Pi^{MZ} form.

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MATERIALS AND METHODS

Pi phenotyping was done by discontinuous acid starch electrophoresis followed by counterelectrophoresis of the starch block into agar containing goat antihuman alpha$_1$-antitrypsin antiserum, as described by Fagerhol and Laurell.[6] The alpha$_1$-antitrypsin concentration was measured by an immunochemical technique.[12]

Hepatic transplantation was performed as reported previously.[20, 21] Liver specimens were prepared for light and electronmicroscopy, as described elsewhere.[20] In addition, horseradish peroxidase labeled antibody to alpha$_1$-antitrypsin and periodic acid Schiff reagent after diastase digestion were used.

CASE REPORT

A 16-year-old Caucasian girl (OT 74) with HB$_s$ Ag negative, coarsely nodular cirrhosis was treated by orthotopic liver transplantation on Nov. 16, 1973. She made an uneventful recovery from her moribund preoperative state and was in good health for more than 1½ years. Graft function then

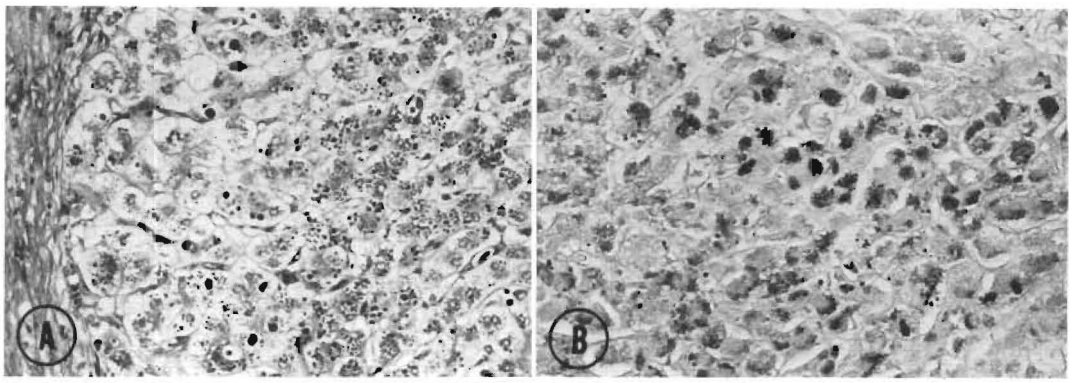

Fig. 1. Sections of the patient's own cirrhotic liver from Case OT 74. *A*, Treated with periodic acid Schiff reagent after digestion with diastase. Stained cytoplasmic globules of varying size are present. (Original magnification ×250.) *B*, Reacted with rabbit antihuman alpha$_1$-antitrypsin serum by the three layer immunoenzyme technique and counterstained with methyl green. The result is positive. (Original magnification ×250.) (From Palmer, P. E., DeLellis, R. A., and Wolfe, H. J.: Immunohistochemistry of liver in alpha$_1$-antitrypsin deficiency. A comparative study, Am. J. Clin. Pathol. **62:** 350, 1974.)

deteriorated steadily to the point that on Feb. 17, 1976, 27 months after the first liver replacement, retransplantation became necessary. Five weeks later, after a stormy postoperative course, she died of pulmonary insufficiency.

PATHOLOGIC STUDIES

The diagnosis of the original liver disease was carried as end stage chronic aggressive hepatitis until review of the case more than a year later. The correct diagnosis for the cirrhotic liver was established by light microscopy of sections stained with periodic acid Schiff reagent after diastase digestion and by immunoelectron microscopy (Fig. 1).

The histopathologic features in consecutive biopsies of the first homograft represented a combination of subacute and chronic rejection. Following a mild rejection episode, the graft developed centrilobular cholestasis with bile "thrombi." Over the next few months some of the hepatocytes became swollen and their arrangement became disorderly. The amount of portal connective tissue increased and septa began to subdivide the liver lobules. About 2 years after the acute rejection episode, the homograft became cirrhotic (Fig. 2, *A*) and 3 months later had to be removed.

The second homograft was not rejected and when the patient died the only abnormality of the liver was some fatty infiltration (Fig. 2, *C*). There was no accumulation in either homograft at any time of the distinctive eosinophilic material which is diastase resistant and detected with the periodic acid Schiff reagent and by immunoelectron microscopy with peroxidase labeled antibody to alpha$_1$-antitrypsin (Fig. 2, *B* and *D*).

SEROLOGIC STUDIES

A saved peroperative serum sample from the recipient contained 55 mg. per 100 ml. of alpha$_1$-antitrypsin; the phenotype was Pi^{ZZ} (Table I). A serum sample from the first organ donor had a normal alpha$_1$-antitrypsin phenotype (Table I). After liver replacement, the recipient's alpha$_1$-antitrypsin concentration rose to normal and the phenotype was uniformly Pi^{MM} for the next 27 months. By coincidence, the second homograft came from a donor who subsequently was shown to have the heterozygous Pi^{MZ} phenotype and a correspondingly reduced serum alpha$_1$-antitrypsin concentration (Table I). Following the retransplantation, the recipient's serum again showed the donor's alpha$_1$-antitrypsin phenotype (Table I).

The patient's family was studied. Both parents proved to be Pi^{MZ} heterozygotes, as were the recipient's two siblings. A third sibling subsequently born in April, 1976, also proved to have the Pi^{MZ} phenotype.

DISCUSSION

In 1971 and 1972, Sharp and the transplant team at the University of Minnesota[16, 17] reported the treatment by hepatic transplantation of two children who had liver disease and homozygous alpha$_1$-antitrypsin deficiency. Both recipients died about one month after operation. However, during their brief survivals, they developed normal levels of alpha$_1$-antitrypsin. The Pi phenotypes apparently were not studied.

By virtue of the long period of observation and the

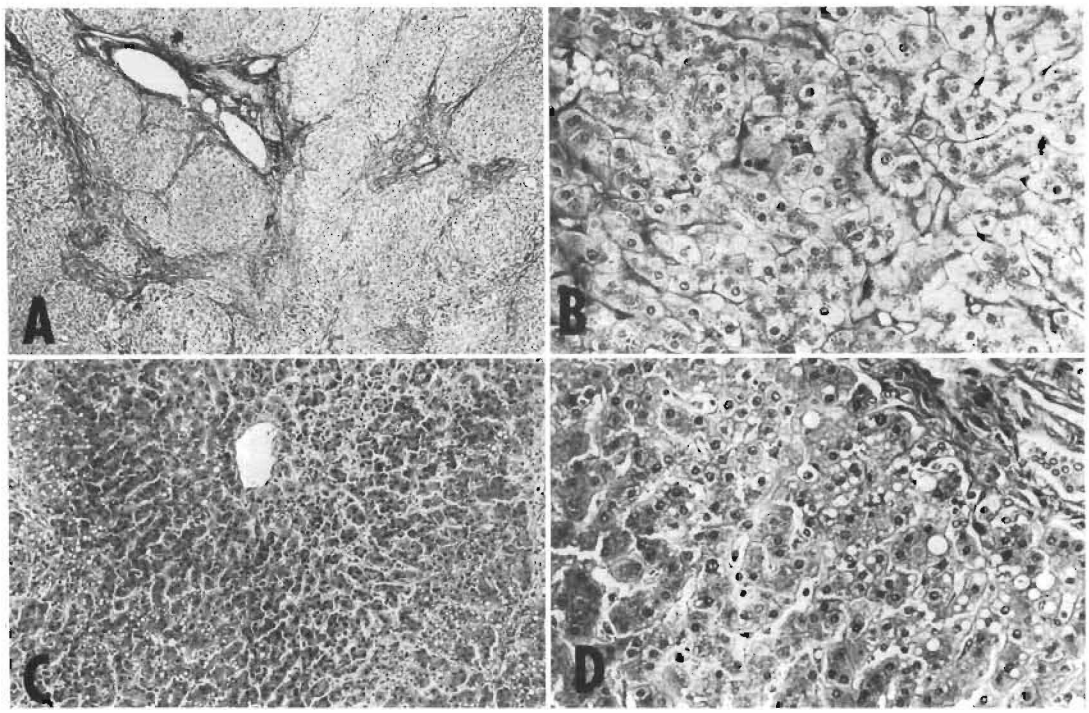

Fig. 2. Histopathology of liver homografts. *A,* Loss of lobular architecture in first liver homograft. (Reticulin stain. Original magnification ×35.) *B,* Swollen hepatocytes arranged in irregular fashion but lacking specific globules in first liver homograft. (Periodic acid Schiff after diastase. Original magnification ×250.) *C,* Normal lobular architecture of second liver homograft. (Hematoxylin and eosin. Original magnification ×150.) *D,* Some fatty infiltration, but no specific globules in second liver homograft. (Periodic acid Schiff after diastase. Original magnification ×250.)

Table I. Alpha$_1$-antitrypsin phenotype and concentration before and after liver transplantation

Alpha$_1$-antitrypsin	*Before transplant*	*First donor*	*After transplant*		*Second donor*	*After retransplant*
			18 mo.	*26 mo.*		
Phenotype	ZZ	MM	MM	MM	MZ	MZ
Concentration (mg./100 ml.) (normal 140 to 470)	55	—	264	256	176	270

occurrence of a second phenotypic transformation after retransplantation, our case provides a more complete dimension, adding another example of the correction of liver-based inborn errors of metabolism by liver replacement to the previously reported ones of Wilson's disease[4, 9] and Niemann-Pick disease.[3]

In our patient the Pi^{ZZ} phenotype of the recipient disappeared promptly after the first transplantation; substituted for it was the donor phenotype Pi^{MM}. The fact that no trace of the pre-existing Pi^{ZZ} glycoprotein remained in the serum demonstrated unequivocally that the liver was the sole source of the alpha$_1$-antitrypsin. Other examples of alpha globulins having an exclusively hepatic origin include haptoglobin[10, 13, 19] and group-specific component.[10]

There was no reason to believe that the homografts were jeopardized because of the recipient's inborn error of metabolism. Instead, the histopathologic pattern in consecutive biopsies of the failing first graft was a combination of subacute and chronic rejection. There were no deposits of alpha$_1$-antitrypsin glycoprotein in either homograft. Accumulation of the Z phenotype glycoprotein in the liver is thought to occur because of the absence of one of the four carbohydrate side chains found in the normal molecule.[2] Thus glycoprotein deposits might be expected with the Pi^{MZ}

phenotype and have been reported in the livers of some heterozygous patients,[5] but without a clear association with liver disease.[14] In our case the second homograft from a Pi^{MZ} donor had not accumulated any visible glycoprotein during either its residence for 25 years in the donor or for 5 weeks in the recipient.

Approximately 10 percent of the population have phenotypes other than Pi^{MM}, of which there are at least 17.[23] The heterozygous phenotype Pi^{MZ} is found in about 5 percent of the population, and the frequency of the homozygous Pi^{ZZ} phenotype has been estimated at 0.1 percent of births.[23] Thus the Pi^{ZZ} phenotype is not a rare form of inborn error of metabolism. Since about 20 to 30 percent of children with this phenotype will develop cirrhosis, Sharp[16] and others[1, 15] have emphasized that all children with liver disease should be evaluated carefully for alpha$_1$-antitrypsin deficiency. The point hardly could be made better than from the events in the life of our patient. She developed chronic liver disease leading to liver failure and transplantation without the diagnosis being made. It was only after a retrospective review of her course, re-examination of the excised native liver, and analysis of her stored preoperative serum had been done that a full explanation for her problems finally evolved.

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