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BRIEF REPORT

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Recurrent postinfantile syncytial giant cell hepatitis after orthotopic liver transplantation

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Abstract Syncytial giant cell hepatitis is a severe form of hepatitis characterized by diffuse giant cell transformation of hepatocytes. The disease may evolve to chronic cholestatic cirrhosis necessitating liver transplantation. We report the case of an adult liver transplant recipient presenting with early recurrent disease without concomitant clinicobiochemical syndrome. Early recurrence of giant cell hepatitis after liver transplantation favors the hypothesis of a transmissible agent as the etiology of the disease. Routine follow-up liver biopsy is necessary in these cases in order to gain more information about the precise incidence and aggressivity of disease recurrence in the allograft.

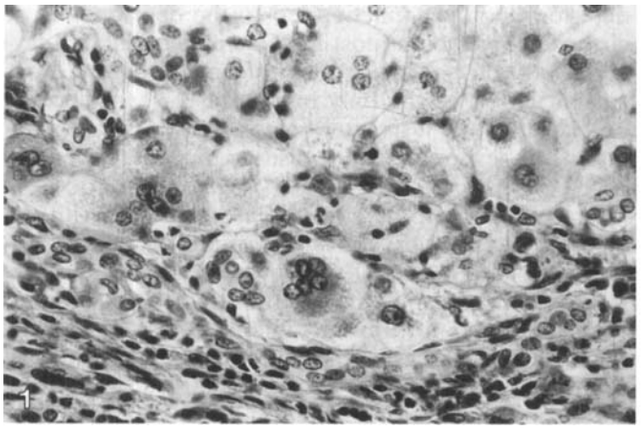
Key words Giant cell hepatitis, liver transplantation · Syncytial cell hepatitis, liver transplantation · Postinfantile giant cell hepatitis, liver transplantation · Liver transplantation, postinfantile giant cell hepatitis

Introduction

Syncytial giant cell hepatitis (SGCH), a commonly described injury in neonatal liver disorders, is rarely described after infancy [1, 3, 13]. The precise etiology is still unknown [3, 8], but indirect evidence exists for its infective and/or autoimmune nature [1, 3, 10, 11]. If that is the case, recurrent disease in the allograft is to be expected. We report the case of an adult patient presenting with early, but asymptomatic, recurrent disease after liver transplantation (LT).

Case report

In March 1991, a 15-year old male presented with marked asthenia and jaundice in the presence of a significant rise in transaminases (AST/ALT were 20 times higher than normal). Anamnesis did not reveal the use of hepatotoxic drugs. A complete virological examination was done: IgM and IgG anti-HAV, HBsAg, IgM anti-HBc, HBV-DNA (dot blot), anti-HCV, HCV-RNA (nested PCR with primers in region 5'), anti-EBV, and anti-HSV were all negative; IgG antibodies against measles (ELISA), mumps (ELISA), respiratory syncytial (complement fixation), and parinfluenza virus type 1 (complement fixation) were positive. Inoculation of a chim-



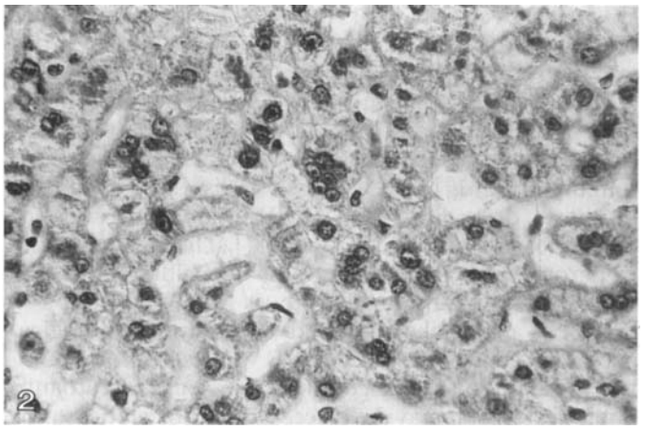


Fig. 1 Histology of explanted native liver showing nodules delimited by fibroinflammatory septa, thereby disrupting the limiting plate, as well as numerous swollen, giant hepatocytes with a finely granular cytoplasm (H&E, × 520)

Fig. 2 Biopsy performed 53 months after transplantation showing multiple, multinucleated hepatocytes. There was no cholestasis or cellular necrosis and only mild inflammatory infiltration (H&E, × 520)

panzee with a liver homogenate of the liver biopsy did not disclose, in the absence of any growth, a viral etiology of the disease. A 3-month steroid treatment (prednisolone 25 mg/day) was unsuccessful and a biopsy taken in October 1991 showed cirrhosis. Two-month ribavirin (1 g/day) as well as alpha interferon (3 million units, three times a week) therapies were unsuccessful. Throughout this period, transaminases fluctuated between 4 and 15 × normal values.

In July 1992, the patient presented with a severe cholestasis. The liver biopsy showed cirrhosis with some periseptal necroinflammatory activity and with multiple giant hepatocytes. Electron microscopy confirmed the presence of multiple, multinucleated syncytial cells containing 20–40 nuclei. The cytoplasm of these giant hepatocytes contained pleiomorphic spherical particles identical to those reported by Koff [7] and Phillips et al. [11]. In September 1992, the patient was hospitalized because of icteric decompensation. Total and direct bilirubin were 27 times normal values; AST and ALT were 10 times normal and gamma glutamyl transferase levels 2 times normal. An aminopyrine breath test confirmed severe liver dysfunction (0.18%; normal value ≥ 2.8%). Autoantibodies and complete virological testing were repeatedly negative, and so the diagnosis of giant cell hepatitis was made.

In April 1993, the patient underwent a blood group-identical, piggy-back liver transplantation at the age of 17 years. Surgery was uneventful and he was extubated immediately after the operation. There were three HLA B-DR mismatches; crossmatch was negative. Immunosuppression consisted of cyclosporin, azathioprine, and methylprednisolone. The hepatectomy specimen, weighing 850 g, showed a micronodular cholestatic cirrhosis. The fibrotic septa revealed severe bile duct proliferation as well as marked lymphoplasmocytic inflammatory infiltration. The nodules consisted of irregularly displayed hepatocytic clusters. The hepatocytes showed marked giant cell transformation, containing up to ten superimposed nuclei. Mallory's hyaline bodies and multiple ballooning hepatocytes containing eosinophilic deposits were seen at the periphery of several cirrhotic nodules (Fig. 1). Immunohistochemical examination using an immunoperoxidase technique for CMV, HSV, HBV, and monoclonal antibody testing against parainfluenza virus I, II, and III (Clonatec, Paris, France) were negative, as were serum HBV-DNA (Boehringer, Mannheim, Germany), HCV-RNA, and HGV-RNA.

On the 2nd post-transplant day, the patient had fever (40°3 C) and developed acute, bilateral, pulmonary edema necessitating immediate artificial ventilation. A liver biopsy done the day after showed mononuclear portal tract inflammatory infiltration. This finding, together with the development of severe thrombopenia (15.000/mm^3), justified treatment of rejection with five boluses of 200 mg methylprednisolone. Biopsies taken on days 8 and 18 showed a vanishing bile duct syndrome. The histological picture could not be reversed by switching to tacrolimus, so the patient was listed for retransplantation. Bilirubin increased to 60 times the normal level; peritoneal dialysis and temporary discontinuation of tacrolimus was necessary because of acute renal failure. On day 36 (11 May 1993), he underwent a successful isogroup piggy-back liver retransplantation. The postoperative course was uneventful, except for a moderate rejection on day 21, which was treated with one bolus of 1000 mg methylprednisolone.

Follow-up liver biopsies performed in October 1994 (17 months post-LT) and October 1997 (53 months post-LT; Fig. 2) revealed multiple, multinucleated hepatocytes in the presence of some segmental lymphocytic portal tract infiltration. Biochemical parameters (bilirubinemia 0.8 mg/dl, AST 12 IU/l, ALT 6 IU/l, and GGT 9 IU/l), as well as autoantibodies and echography pattern, remained normal throughout the entire post-transplant period. All virological tests except for HGV-RNA remained negative.

Steroids were progressively reduced and finally withdrawn 31 months post-LT. The patient did not receive ursodeoxycholic acid at any time during the transplant period. Fifty-three months post-LT, the patient was doing very well under tacrolimus monotherapy. His Karnovsky score was 90% and he started his studies in law.

Discussion

Syncytial giant cell hepatitis is a rare but severe form of hepatitis that can occur at any age [1, 3, 8, 10, 11]. It is characterized by diffuse giant cell transformation of hepatocytes with a variable degree of hepatocytic ne-

crosis and liver fibrosis [13]. Its real incidence is probably underestimated as the number of giant cells varies greatly from one tissue specimen to another [3].

The disease is best known as a severe neonatal hepatitis. In older children and adults, SGCH is uncommon; it is said to represent a nonspecific tissue reaction to autoimmunity, drug (nuclear) toxicity, disorders of bile salt synthesis, or to HBV, HCV, HIV, papilloma virus, or paramyxovirus infections [2, 10, 11]. The causative role of paromyxovirus, stated in 1991 by Phillips et al., has been questioned by many authors [2, 6, 7, 10, 11, 14]. SGCH is more likely related to different etiological agents and may have an acute, as well as a chronic, clinical presentation [1, 2, 6, 8]. In the presence of autoantibodies, steroids may be successful; cholestatic forms may be improved by ursodesoxycholic acid [1]. Spontaneous remission occurs in up to 25% of the cases; 30%–50% of the patients progress to severe cholestatic micronodular cirrhosis, ultimately leading to elective or even urgent liver transplantation [1, 3, 8, 10, 11].

The apparently successful treatment of SGCH by transplantation has been challenged by the Pittsburgh report stressing the universal, and nearly always aggressive, recurrence of allograft disease [10, 11]. All five patients reported had disease recurrence, from 1 to 21 months post-LT, with clinical and pathological presentation similar to that of the native disease. Rapidly deteriorating liver function led to the development of cirrhosis 4–18 months post-LT. One patient did well several months following re-LT, performed because of recurrent cirrhosis; the only long-term (6-year) survivor had normal liver tests after having refused retransplantation for severe recurrent disease diagnosed 1 month post-LT.

Early recurrent allograft disease, together with the possible detection of intracytoplasmic structures consistent with paramyxoviral nucleocapsides and the detection of human papilloma viral DNA, lend support to the hypothesis of a transmissible agent as the etiology of SGCH [10, 11]. If transplantation is indicated, one should be aware of the possibility of early aggressive recurrent disease. Routine allograft biopsy will shed light on the real incidence and importance of recurrent disease. SGCH may indeed be present in the absence of any clinicobiochemical syndrome.

As ribavirin has been shown, in some studies, to be effective in treating SGCH, its prophylactic use may reduce the likelihood of allograft recurrence [4, 5, 9, 12]. The best treatment for severe, recurrent disease is one that is tailored to the clinical and biochemical evolution of the patient. Retransplantation should be limited to those patients presenting a longlasting course ultimately leading to liver failure.

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