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Pediatric liver transplantation for primary hepatocellular carcinoma associated with hepatitis virus infection

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Abstract. We report two cases of early primary hepatocellular carcinoma (PHC) in children, after probable maternal transmission of hepatitis B, that were treated with orthotopic liver transplantation (OLT). Both children were 8.5 years old and had elevated levels of serum alpha-fetoprotein. The diagnosis of PHC was made at 8 years and confirmed histologically. Serum hepatitis B surface antigen (HBs Ag) was detected in the mothers and suggested vertical transmission. An attempt at complete liver tumor resection failed, leading to OLT. In order to prevent recurrence of the hepatitis B virus (HBV) infection, hepatitis B immunoprophylaxis was used. Two years after OLT, one child presented with recurrent HBV infection. No tumor recurrence was observed at follow-up in either of the patients. From these two cases we conclude that (1) HBV infection may play an important causal role in PHC in children, with an even shorter incubation period than that in adults; (2) close follow-up is needed for children who are HBs Ag-positive carriers; and (3) liver transplantation should be proposed early after the diagnosis of PHC, when tumor resection is not feasible.

Key words: Liver transplantation, hepatocellular carcinoma – Hepatocellular carcinoma, liver transplantation – Hepatitis, viral, liver transplantation – Hepatitis, viral, hepatocellular carcinoma

Introduction

The relationship between chronic hepatitis B virus (HBV) infection in adults and primary hepatocellular carcinoma (PHC) is well recognized [3]. In pediatric patients, this association was underestimated for a long time. This was due to the general belief that the minimum incubation period between the time of infection by HBV and the development of PHC was 20–40 years [4, 19]. Only a few reports of PHC in children associated with HBV infection have been published [11, 26]. We report two documented cases of PHC in childhood, after probable maternal transmission of HBV, that were treated with orthotopic liver transplantation (OLT).

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Case reports

Case 1

A 14-month-old boy underwent hepatic tests for positive serum hepatitis B surface antigen (HBs Ag), which had been detected in his mother. His serum transaminase levels were high. Serum HBs Ag and hepatitis Be antigen (HBe Ag) were positive. The family's serum HBV tests showed that the mother was positive for both HBs and HBe Ag. The child's liver biopsy specimen showed features of chronic active hepatitis and cirrhosis. Biannual screening for PHC using alpha-1-fetoprotein (AFP) levels (tested by radioimmunoassay) and liver ultrasound (US) examination was carried out.

The boy was referred to our center at the age of 8 years for elevated AFP (five times the normal value) associated with two liver tumors in the right lobe at US examination. The work-up, using abdominal and thoracic computed tomographic scans (CT), angiography, and magnetic resonance imaging (Fig. 1), confirmed the liver tumors in segment VI and did not show extrahepatic lesions. Serum

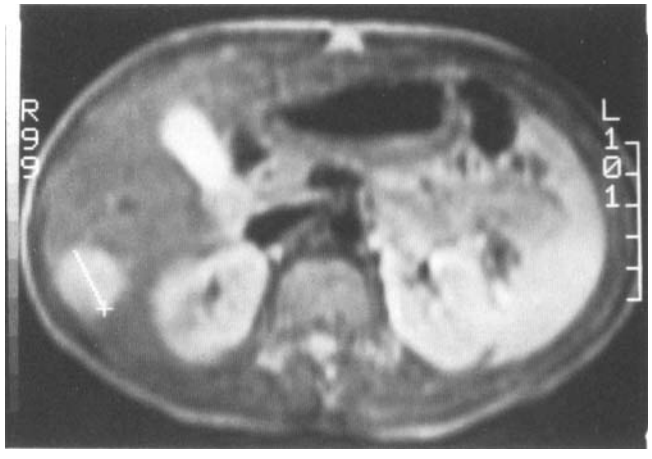

Fig. 1. Case 1. Liver tumor in segment VI on magnetic resonance imaging

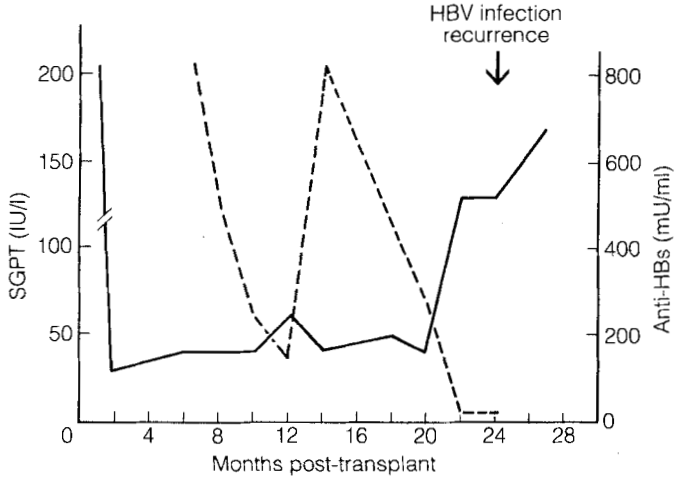

Fig. 2. Case 1. Outcome of transaminases (——) and anti-HBs (– –) after liver transplantation

HBV DNA was negative. At laparotomy, despite a peroperative US examination, only one tumor could be found and this was removed. The pathology of the resected specimen showed one single mass. Histologic examination showed a PHC of the trabecular type. Two weeks after the operation, a second abdominal CT scan showed three other liver tumors (two in segment VII, one in segment IV). It was then decided to perform an OLT, and this occurred 7 months later. The donor was negative for all serologic tests for HBV. HLA matching was A11,24 B35,51 DR2,5 for the recipient and A28,- B18,15 DR3,5 for the donor. Hepatitis B immune globulins were administered during the anhepatic phase of the operation, as described below. Histologic examination of the diseased liver showed three PHCs of the trabecular type with cirrhosis in the rest of the liver. Lymph nodes were free of tumor. The immunosuppression regimen consisted of cyclosporin, steroids, and, for a week, azathioprine, according to Bernard et al. [7]. At discharge, 1 month after the operation, all serum liver tests were normal, HBs Ag was absent, and serum antibodies (anti-HBs) were at 230 mU/ml (Fig. 2).

Two years post-transplantation, anti-HBs suddenly dropped to less than 30 mU/ml, with an increase in serum transaminase levels. SGPT levels increased up to three times the normal value (Fig. 2). HBs Ag reappeared in the serum, and serum HBV DNA became positive. A liver biopsy showed portal fibrosis and intracytoplasmic "ground-glass" inclusions typical of HBs Ag. Steroid doses were reduced from 25 to 22 mg every 2 days. The cyclosporin dose was not changed (7 mg/kg per day). Anti-HBs administration was discontinued.

At 27 months post-transplantation, the child is doing well (Table 1). Serum transaminase levels are six times the normal value. AFP, prothrombin time, serum alkaline phosphatase, and bilirubin levels are normal.

Case 2

An 8-year-old girl was referred for an isolated right upper quadrant abdominal mass. US examination and abdominal CT scan showed a liver tumor (50 × 42 × 25 mm) in segment IV. Her serum AFP level was 50000 IU/ml (normal < 16). The work-up did not show distant metastases. The mother was positive for HBs Ag and anti-HBc. Our patient, positive for HBs Ag, was negative for serum viral DNA. She underwent a segmentectomy with removal of segment IV. Frozen sections were not requested. The histologic examination revealed a PHC of the trabecular type. Chronic persistent hepatitis without cirrhosis was found in the rest of the liver. Because the resection margin was involved by the tumor and vascular emboli were present in the tumor, an OLT was performed 4 months later. The donor was negative for all serologic tests for HBV. HLA matching was A1,3 B14,37 DR7,- for the recipient and A2,28 B35,- DR2,5 for the donor. HBV immune prophylaxis was also carried out.

Postoperative immunosuppression consisted of a combination of cyclosporin, steroids, and azathioprine. The postoperative course was uneventful. Twenty-four months after transplantation the child is doing well with normal serum hepatic tests and AFP (Table 1). Her serum anti-HBs level is 400 mU/ml. HBs Ag and serum HBV DNA are absent.

Passive immunoprophylaxis after OLT

During the anhepatic phase of transplantation, both children received 6000 IU of specific anti-HBs immune globulins (CNTS, France). The same dose was administered by intravenous infusion every day, from day 1 to day 6 after OLT. In the outpatient clinic, the children received 5000 IU of anti-HBs immune globulins every 7 weeks. The goal of this treatment was to keep the serum anti-HBs level higher than 100 mU/ml. After transplantation, both children were screened for HBs Ag, anti-HBs, and HBV DNA at the end of the 1st postoperative week. Serum anti-HBs was measured weekly, and serum HBs Ag, HBe Ag, and HBV DNA were screened a month after OLT and then every 7 weeks.

Discussion

PHC is a rare tumor in children. The prevalence of primary hepatic neoplasms is estimated to be 0.5%–2.0% of pediatric tumors, with PHCs accounting for 20% of them [2, 17, 20].

Beasley [3, 5] has shown in adults that chronic HBs Ag carriers have a 200 times greater risk of developing PHC than the general population. In most studies, patients developing PHC have had hepatitis B infection for 20–40 years [4, 25], suggesting a necessary latent period as long as 20–40 years from the time of HBV infection to PHC occurrence.

The first studies reporting an association between HBV infection and PHC in childhood were published in the early 1980s [6, 15, 24]. Pediatric PHCs are associated with perinatal transmission of the HBV from HBs Ag-positive carrier mothers in 70%–90% of cases [13, 26]. Most pediatric PHCs associated with maternal transmission of HBV occur between 6 and 8 years of age [11], as in our two cases, although the youngest child reported

Table 1. Children's characteristics. HBV, Hepatitis B virus infection; AFP, serum alpha feto-protein level; PHC, primary hepatocellular carcinoma

Cases	Prior to transplantation				Transplantation			After transplantantion			
	HBV Transmission	Age at diagnosis (years)	Serum HBV DNA	AFP	Age (years)	PHC	HBV Prophylaxis	Follow-up (months)	HBV Infection recurrence	Serum HBV DNA	AFP
Case 1	Vertical	8	–	5N	8.5	Trabecular	+	27	+ (24 months)	+	–
Case 2	Vertical	8	–	300N	8.5	Trabecular	+	24	–	–	–

in the literature was 3 years old [10]. Despite the lack of documentation of maternal infection at the time of delivery, perinatal HBV transmission could be presumed in our two cases.

Wu et al. [26] have shown that the average survival after diagnosis of PHC 4.7 months in children. Thus, surgical tumor removal is the only chance for a long-term cure. Data available from the literature provide little information about the concurrent application of liver resection and transplantation for PHC. Ringe et al. [22] have shown that resection for PHC without coexisting cirrhosis resulted in a survival of 45% at 5 years, compared to 12% after liver transplantation. However, this is less favorable than the 88% 2-year survival observed in patients receiving a liver graft for benign end-stage liver diseases and who had small incidental hepatocellular carcinoma [16]. In cases of coexisting cirrhosis, Adson [1] has pointed out that multicentric growth was quite common. He suggested that the oncogenic risk of viral hepatitis could only be reduced by total hepatectomy. All of these arguments may favor early OLT instead of limited resection, even though PHC may or may not be associated with cirrhosis. Two years after transplantation our children are alive and tumor-free. Nevertheless, we cannot exclude late tumor recurrence, as currently the results of OLT for PHC show a tumor recurrence rate of 65%–70% [8, 21]. This high rate of tumor recurrence and the related shortened life expectancy may be due to the fact that, at present, partial hepatectomy is considered first, whereas OLT is applied to cases of nonresectable or recurrent tumors [22].

After OLT the 2-year actuarial incidence of HBV reinfection in chronic HBs Ag-positive carriers is estimated to be about 90% [12, 14] without immunoprophylaxis. The incidence of HBV reinfection of the liver graft after OLT is reduced by long-term passive immunization, culminating in a 2-year actuarial incidence of HBV reinfection of 29% [12]. Samuel et al. [23] and Lauchart et al. [18] have shown that the presence of serum HBV DNA prior to transplantation is an accurate predictor of risk of recurrent post-transplant infection, as recrudescent HBV infection is observed in 96% of HBV DNA-positive patients, compared with 29% of those who are HBV DNA-negative. In their series, immunoprophylaxis failed to prevent reinfection in most patients who had evidence of active viral replication with circulating HBV DNA prior to OLT. Our children were both HBV DNA-negative prior to transplantation. However, one presented with recurrent post-transplant infection. In this child, the onset delay (2 years) of reinfection was longer than the mean interval of 9.1 months reported by Samuel et al. [23]. They also suggested that viral reinfection of the graft may arise from extrahepatic sites, rather than from immediate infection of the graft by circulating HBV. Calmus et al. [9] have suggested that compatibility in HLA class I matching may be responsible for recurrent post-transplant HBV infection. In our patient with recurrent post-transplant infection, donor and recipient were not compatible in HLA A and B.

Our cases and previous studies suggest that HBV infection may play an important causal role in PHC in children, with an even shorter incubation period than that in adults. For children who are HBs Ag-positive carriers, a close follow-up using AFP and US examination, performed at least twice a year, may lead to early PHC diagnosis. In these cases, OLT should be considered early, either first or when tumor resection is not feasible. Passive immunoprophylaxis should be performed after OLT in HBs Ag-positive children, particularly in those without serum HBV DNA prior to transplantation.

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