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Case Report

Orthotopic liver transplantation for Hepatitis C infection: the best Christmas present?

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SUMMARY

We report the case of a 60-year-old man with mild Christmas disease, Factor IX 10% of normal, who developed chronic hepatitis C infection after receiving coagulation factor concentrates. Subsequently he developed encephalopathy and liver failure and was referred for liver transplantation. Following transplantation, Factor IX levels rapidly normalised and have remained so, representing a phenotypic cure of his Christmas disease.

CASE REPORT

The patient originally presented in 1971 (aged 35 years) with an episode of prolonged bleeding from the site of a dental extraction. Investigations led to the diagnosis of mild Christmas disease (Haemophilia B). Over subsequent years he was given fresh frozen plasma and then intravenous coagulation factor concentrates. In 1978, as part of pre-operative management prior to haemorrhoidectomy he was given coagulation factor concentrates, and two weeks following this he developed clinical jaundice with the maximum bilirubin concentration rising to 100 mg/l. It is assumed that the coagulation factor concentrates were infected with hepatitis C virus. Liver function tests were normal pre-operatively. The jaundice rapidly resolved although his liver function tests remained abnormal. He had no other risk factors for hepatitis C infection or for the development of end-stage liver disease.

In May 1995 he presented with haematemesis and melaena. Splenomegaly was noted on examination, and upper gastrointestinal endoscopy revealed large oesophageal varices which were treated by a course of injection sclerotherapy. He suffered several episodes of encephalopathy without evidence of further gastrointestinal bleeding, electrolyte imbalance or infection. In 1996 he developed further episodes of encephalopathy and bleeding varices which were again treated by injection sclerotherapy. His clinical course was complicated by the development of ascites which resolved with spironolactone. He continued to have episodes of intermittent confusion and poor energy and was managed with oral spironolactone, neomycin and lactulose. Liver biopsy was not performed. He was unable to tolerate alpha-interferon treatment on account of side-effects.

Hepatitis C antibody testing was positive and hepatitis C RNA by PCR (Polymerase Chain Reaction) was persistently positive with viral subtype 3a. *HbsAg* negative; *HbeAg*, *HbeAb* were negative. *HBV* core *IgG* was not performed. HIV antibody test was negative. Autoimmune screen revealed anti-smooth-muscle antibody in low titre. Haemoglobin was reduced at 10.0 g/dl, white cell count 4.1 x 10^9/l, platelets 163 x 10^9/l. Liver function tests were as follow: albumin 29 g/1, *AST* 56 U/1, *ALP* 216 U/l, bilirubin 28 mg/l, alpha-fetoprotein normal. Creatinine clearance

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was normal (86 mls/min). Pulmonary function tests and echocardiogram were normal. Aminoacid profile at the time of encephalopathy revealed increased levels of tyrosine, phenylalanine and methionine, and normal levels of valine, leucine and isoleucine. Copper studies and alpha-1-antitrypsin were normal. Ultrasound of the abdomen revealed patency of the portal vein. CT brain scan was normal. Electro-encephalogram revealed mild generalised abnormality with slight temporal preponderance.

He was referred to King's College Hospital, London, where he underwent an orthotopic liver transplantation in October 1997. On the second post-operative day he was found to have normal Factor IX levels. He was subsequently treated with cyclosporin, azathioprine, prednisolone and sucralfate and remains well at six-month follow-up. Hepatitis C RNA detected by PCR is positive post-transplantation, and Factor IX levels remain normal.

DISCUSSION

It is well-recognised that most haemophiliac patients who have been given coagulation factor concentrates prior to 1985 are at risk of hepatitis C infection. Interferon is the main treatment currently available for chronic hepatitis C infection and is commenced after a liver biopsy confirms significant inflammatory changes combined with evidence of active viral replication. The risks of liver biopsy, in particular haemorrhage, obviously are accentuated in haemophiliacs who require coagulation factor concentrates prior to the procedure, therefore interferon treatment is often given without a biopsy being undertaken. Liver biopsy may be carried out in haemophiliacs who are empirically treated with interferon but who are unable to tolerate the full course of treatment or if the patients' symptoms suggest that they may have significant liver disease which is not indicated by liver function tests. The main limitations of interferon treatment are adverse effects including poor energy and flu-like symptoms as in this case. Combination treatment is a possible treatment option for the future and further studies are currently underway with amantidine and ribavirin with interferon.

Haemophiliac patients with chronic hepatitis C infection have a cumulative risk of progressing to liver cirrhosis in 1.7% at 10 years and 19.8% at 20 years[1] and liver transplantation may be required. Successful liver transplantation in humans with haemophilia was initially described in one patient with severe haemophilia A (Factor VIII deficiency) in 1985.[2] The procedure is safe providing that adequate intra-and immediate post-operative coagulation factor replacement is given to avoid bleeding complications and there does not appear to be an excessive transfusion requirement.[3] There are reports of three patients with Haemophilia B (4-6), 10 patients with Haemophilia A (3, 4, 7-9) and one patient with combined factors VIII and IX deficiency[10] who have received liver transplants in the literature. Data on the survival and length of cure of such patients is limited. One report documents survival of 12 months post-transplantation and sustained factor concentrations.[4] There is one report of a patient who died intra-operatively which was related to technical difficulties of graft insertion[9] and one late mortality due to the development of acquired immunodeficiency syndrome,[8] another complication of multitransfused haemophiliacs.

Liver transplantation has been used in the treatment of genetic diseases in patients with no significant liver disease.[11] A case can be made for liver transplantation prior to the development of liver failure in haemophiliac patients with hepatitis C infection in view of the additional benefits of a phenotypic cure of the clotting abnormality.[3] However, this must be viewed in the light of the present shortage of organ donors and the impact on other patients with end-stage liver disease. The mechanism of cure of the coagulation deficiency relates to the fact that the liver is the source of synthesis of the vitamin K dependent coagulation factors (including Factor IX) and since the graft originated from a non-haemophiliac patient there is a phenotypic cure of the coagulation deficiency.

The main long-term problem with liver transplantation for hepatitis C induced cirrhosis is allograft reinfection with HCV, which usually runs a benign course[12] although it may progress to cirrhosis within 1-2 years.[13] The time taken for the restoration of normal coagulation factors may be as short as 12 hours[4] and a sustained response at 72 hours confirms de novo synthesis of clotting factors by the graft. Further follow-up is required to determine if there is a sustained cure of the haemophilia and to see the outcome of the continuing HCV infection.

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