A case of giant cell hepatitis recurring after liver transplantation and treated with ribavirin

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CASE PRESENTATION
A 42-year-old patient underwent OLT in June 1990 for GCH with cirrhosis. Before liver transplantation, he tested negative for hepatitis B surface antigen (HBsAg), hepatitis B surface antibodies, hepatitis B core antibodies, hepatitis C virus antibodies, Epstein Barr virus (EBV) (viral capsid antigen and EBV-determined nuclear antigen) antibodies, antihuman immunodeficiency virus antibodies, antimitochondrial antibodies, antinuclear antibodies and smooth muscle antibodies. He proved later to be hepatitis C virus RNA-negative as well. He was immune to cytomegalovirus. GCH recurred twice after OLT and was treated with ribavirin.

BRIEF COMMUNICATION
Z Hassoun, B N’Guyen, J Côté, et al. A case of giant cell hepatitis recurring after liver transplantation and treated with ribavirin. Can J Gastroenterol 2000;14(8):729-731. A patient who underwent orthotopic liver transplantation for giant cell hepatitis with cirrhosis and in whom giant cell hepatitis recurred twice after orthotopic liver transplantation is reported. He was treated with ribavirin with an excellent result. The literature on this subject is reviewed. This observation clearly confirms the efficacy of ribavirin for the treatment of giant cell hepatitis, thus providing evidence for its viral origin.

Key Words: Cirrhosis; Giant cell hepatitis; Liver failure; Orthotopic liver transplantation; Ribavirin

Giant cell hepatitis (GCH) is a relatively common pathological finding in neonates and infants, and is associated with a variety of conditions, such as intra- and extrahepatic biliary atresia, infectious or metabolic diseases, and the so-called neonatal hepatitis (1). It has occasionally been described in adults, with features suggesting a viral origin and a rapidly progressive course (2). Its recurrence after liver transplantation has been reported (3), as has its treatment with ribavirin after orthotopic liver transplantation (OLT) in one patient (4). We report a patient in whom GCH recurred twice after OLT and was treated with ribavirin.

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Figure 1) Biopsy specimen showing recurrence of giant cell hepatitis on the second transplanted liver after the withdrawal of ribavirin. Numerous multinucleated giant cells (arrowheads) are visible on this photomicrograph, as are multiple areas of lobular inflammation.

Figure 2) Biochemical profile of the patient after the second liver transplantation, showing the evolution of serum alanine aminotransferase (ALT) and bilirubin with respect to ribavirin treatment. Time 0 is the time of the second orthotopic liver transplantation (OLT)

GCH (Figure 1), and ribavirin was reintroduced with a drastic improvement in LFT results, which normalized completely in August 1999 and have remained normal with continued ribavirin treatment (Figure 2). A control liver biopsy performed in May 1999 demonstrated a marked decrease in portal and lobular inflammation, and in the number of giant cells.

DISCUSSION

GCH is characterized by the presence throughout the liver of numerous enlarged multinucleated hepatocytes with abundant cytoplasm (1). It is a nonspecific reaction in neonates and infants with various liver diseases. The term ‘post-infantile GCH’ was coined by Thaler (5) to describe this histological finding in the older patient. In 1991, Phillips et al (2) described 10 patients who had syncytial GCH, with a severe course and a poor outcome. Structures resembling the nucleocapsids of paramyxoviruses were seen on electron microscopy, but the putative virus could not be identified. In 1993, Roberts et al (6) reported an infant with severe neonatal GCH who was treated effectively with a 10-day course of intravenous ribavirin. In 1994, Pappo et al (3) described five patients who had GCH that recurred after liver transplantation. In 1997, Durand et al (4) reported an adult patient with subfulminant GCH leading to OLT and recurring in the transplanted liver. This patient was treated with two 21-day courses of intravenous ribavirin; LFT results and liver histology normalized. In 1998, Fimmel et al (7) performed elaborate molecular biology manipulations on the liver tissue of a patient affected by GCH and obtained a positive signal on in situ hybridization studies with a probe directed against the measles fusion protein. Taken together, these observations suggest that a yet unidentified virus, related to Paramyxoviridae, may play a role in the pathogenesis of GCH.

Some authors have suggested, however, that other etiological factors may be implicated in GCH, based on retrospective case reviews and case reports (8-14). The patients described had a variety of associated conditions, including autoimmune features, with or without overt autoimmune conditions. Some patients described had decided lupus or collagen vascular disease, others had subacute sclerosing panencephalitis, and others had a variety of other conditions. Phillips et al (2) described 10 patients who had syncytial GCH, with a severe course and a poor outcome. Structures resembling the nucleocapsids of paramyxoviruses were seen on electron microscopy, but the putative virus could not be identified. In 1993, Roberts et al (6) reported an infant with severe neonatal GCH who was treated effectively with a 10-day course of intravenous ribavirin. In 1994, Pappo et al (3) described five patients who had GCH that recurred after liver transplantation. In 1997, Durand et al (4) reported an adult patient with subfulminant GCH leading to OLT and recurring in the transplanted liver. This patient was treated with two 21-day courses of intravenous ribavirin; LFT results and liver histology normalized. In 1998, Fimmel et al (7) performed elaborate molecular biology manipulations on the liver tissue of a patient affected by GCH and obtained a positive signal on in situ hybridization studies with a probe directed against the measles fusion protein. Taken together, these observations suggest that a yet unidentified virus, related to Paramyxoviridae, may play a role in the pathogenesis of GCH.

Some authors have suggested, however, that other etiological factors may be implicated in GCH, based on retrospective case reviews and case reports (8-14). The patients described had a variety of associated conditions, including autoimmune features, with or without overt autoimmune
disease, and hypereosinophilia. In some patients, there was an identifiable cause of liver disease—autoimmune hepatitis, acute hepatitis A or B, chronic hepatitis C or drug exposure. In others, the etiological work-up remained negative. Patients with or without autoimmune features have been treated with immunosuppressive therapy (8, 10-12,14), with favourable results in most cases. Even in untreated patients, the outcome appeared to be much less ominous than that described by Phillips et al (2).

Our patient had the typical histopathological features of GCH, and no cause was found before the first transplantation and after the second one. GCH recurred on the two transplanted livers despite immunosuppression with a triple-drug regimen (prednisone, azathioprine and cyclosporine) and was effectively treated with oral ribavirin. On withdrawal of this antiviral drug, severe recurrence of GCH that responded to the reinitiation of therapy was documented. It might be implied from this observation that GCH was, in this case, related to a transmissible factor that responded to ribavirin and was thus likely to be viral. It is noteworthy that continuous treatment seemed necessary, while short courses of intravenous ribavirin appeared to be sufficient in the two previously published cases (4,6).

CONCLUSIONS

GCH seems to encompass a wide spectrum of liver diseases in adults, as it does in children. A cause may be evident in some cases and absent in others. Autoimmunity and infection with an as yet unidentified virus have been implicated most frequently. Clinical courses are highly variable. In some cases, GCH seems to respond to immunosuppressive therapy and in others to antiviral therapy; sometimes it responds to none of these therapies (15). We present a case that demonstrates clearly the efficacy of ribavirin treatment for GCH and thus adds evidence for its viral origin in some cases.

REFERENCES
