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LETTER TO THE EDITORS

Partial graft recovery following eradication of hepatitis E virus infection after successful islet allograft transplantation

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Hepatitis E virus (HEV) may cause chronic hepatitis and cirrhosis in immunocompromised patients, especially after solid organ transplantation [1–5]. Here, we report on the first documented case of HEV-related chronic hepatitis after islet transplantation (IT) alone in a previously reported patient [6] in addition to the consequences on liver-implanted islet cells.

An athletic 36-year-old man (BMI 25 kg/m^2) with brittle type 1 diabetes received two IT (10 341 IEQ/kg) according to the Edmonton protocol in April (M0) and June (M2) 2005. Insulin-independence was attained 10 days following the second infusion (Fig. 1a) despite a gall bladder puncture requiring cholecystectomy allowing a liver biopsy showing normal islets.

Liver enzyme levels, normal before IT, increased transiently fivefold after each IT, and then increased significantly again from 8 months to 4 years post-IT (Fig. 1b). The patient was asymptomatic, with normal physical examination, and never consumed alcohol. The only drugs he was receiving were sirolimus and tacrolimus, with perfect compliance. Viral hepatitis [HAV, HBV, HCV, HIV, HTLV, cytomegalovirus, herpes, varicella zoster, parvovirus, HHV8, cocksackie, and Epstein–Barr virus (EBV)] detection remained negative except for question-

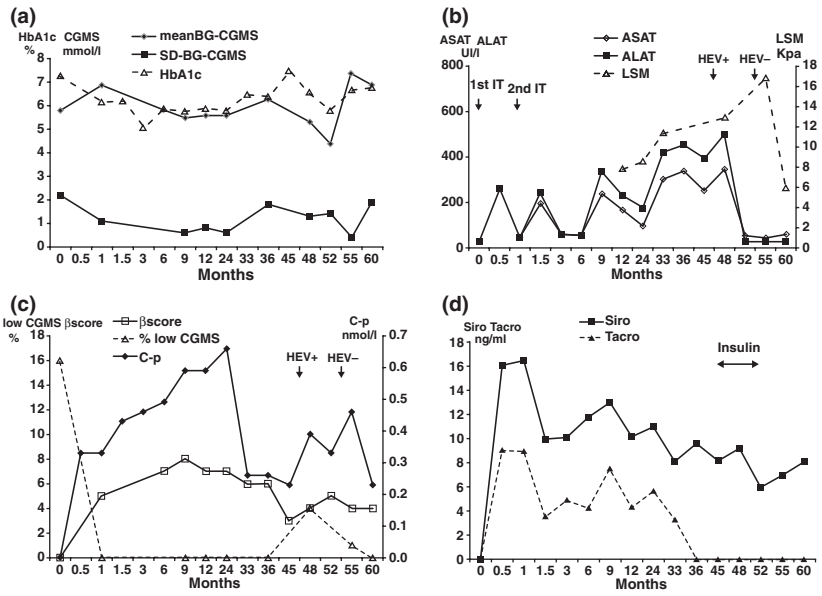

Figure 1 *Patient's 5-year follow-up*: The dates of islet transplantation (IT) and RT-PCR screening for hepatitis E virus (HEV) are indicated on panel B (+: positive screening; –: negative screening). (a) HbA1c (%), mean blood glucose (BG; mmol/l), standard deviation (SD; mmol/l) on continuous glucose monitoring (CGMS; Medtronic MiniMed, Northridge, CA, USA) according to time post-transplantation. (b) *Left ordinate*: Liver enzymes (AST, ALT; IU/l) and *Right ordinate*: liver stiffness measurement (LSM; kPa) assessed with transient elastography (TE, FibroScan) according to time post-transplantation. (c) *Left ordinate*: Percentage of registered time spent below 3 mmol/l on a CGMS record (low CGMS; %) and, beta-score (depending on HbA1c, stimulated C-peptide, fasting blood glucose and insulin or anti-diabetic drugs; normal range 0–8 (0 corresponding to an insulin-dependent type 1 diabetic patient, and 8 to an insulin-independent islet-transplanted patient with HbA1c below 6%), and *Right ordinate*: blood fasting C-peptide level (nmol/l) according to time post-transplantation. (d) Sirolimus and tacrolimus blood levels (ng/ml) according to time post-transplantation; Duration of insulin resume is also indicated.

able fluctuations for EBV IgM. Normal liver MRI, blood lipid, glucose, iron, copper, alpha-1-antitrypsin parameters, and continuous glucose monitoring (CGMS) (Fig. 1 a–c) did not suggest a metabolic origin. The undetectable level of anti-HLA [Luminex, Labscreen Mixed, Ingen, Chilly-Mazarin, France] and GAD, IA2, ICA autoantibodies did not support allo- or autoimmune rejection. Liver stiffness measurements (LSM-FibroScan, Echosens, Paris, France) increased over time (Fig. 1b), suggestive of progressive fibrosis. A second liver biopsy in 2007 (M24) showed portal inflammation with moderate activity (A2), mild portal fibrosis (F1), lymphoplasmacytic infiltrates, and periportal necrosis, suggesting autoimmune hepatitis. However, there were no liver auto-antibodies. A third biopsy in 2009 (M48) was classified as A1F2. Liver toxicity from immunosuppressive drugs was suspected, and tacrolimus progressively switched to mycophenolate (1 g, then 500 mg bid), whereas the daily sirolimus dose was slightly reduced without initial improvement (Fig. 1d). Insulin had to be resumed in January 2009 (M45) as a result of an increase in the HbA1c and a beta-score drop from 6 to 3. Finally, HEV serology showed negative IgG and mildly positive IgM levels (1.6; normal range <1), confirmed at 2.48, then 3.48 in February and March 2009 (M47), respectively and associated with positive viral quantification (RT-PCR). In June 2009 (M50), when the sirolimus level was <7 ng/ml, the liver enzymes and HbA1c returned to normal and the RT-PCR HEV showed negative viral quantification in October (M54), which was confirmed twice. The occurrence of hypoglycemia led to insulin discontinuation with a fall of duration time <3 mmol/l on CGMS, from 4% to 0%, an increase of the beta-score from 3 to 4, and normalization of LSM (Fig. 1). The patient's pre-IT blood sample and one from each of the two donors remained negative on HEV PCR testing.

The first question raised by this case report concerns the difficulty of HEV infection diagnosis that, until recently, had been unrecognized, whereas the specificity of the diagnosis is sometimes confused with CMV and EBV infection [7]. Secondly, the origin of infection remains unknown, and no evidence of HEV infection could be found in the patient's pre-IT blood samples or in those of the two donors. Nevertheless, one of them had just been transfused before death, and a non-negligible prevalence of HEV infection has recently been established among blood donors [8]. Infection by this indirect route is feasible, but it is more likely that the patient, who worked in a water treatment plant, could also have been a healthy carrier or been infected after transplantation. As recently suggested [4,5], the immunosuppressive regimen is probably the revealing factor of infection, in accordance with the resolution of HEV infection with immunosuppressive drug reduction, setting aside the hypothesis of viral transmission via IT. Nevertheless, this last point remains questionable [9], and highlights the problem of xenotransplantation [10].

Questions may also be raised as to why the infection remained relatively steady on one hand, and without major consequences to the insulin-independence state on the other. Indeed, the immunosuppressive regimen seems to act just as a facilitating factor for the disease expression, usually without inducing acute hepatic failure [4]. The increase of liver enzymes linked to viral hepatitis is delayed [4,11], whereas the peak observed just after each IT is a known consequence of portal infusion [12]. In IT, HEV infection could affect the prognosis by increasing insulin resistance or damaging transplanted islets via inflammation or even direct islet viral infection. Indeed, the progressive decrease of islet graft function observed in our patient was very similar to that of the patients transplanted in the same center [6]. There is therefore no proof that HEV speeded up islet destruction, despite the known role of viruses in type 1 diabetes genesis [13]. The patient's metabolic parameters and LSM improved after HEV recovery, rather suggesting a transient islet dysfunction related to inflammation [as found on biopsies] and/or insulin resistance [14].

The last point is the therapeutic strategy. Steroids were avoided because of the lack of an initial diagnosis and because of sustained insulin independence. As a result of the progressive fibrosis and a nonlife-dependent IT, we switched the tacrolimus, which has recently been shown to favor HEV chronic progression, and decreased the immunosuppression level, which eventually proved to be the right choice [2–4]. The difficulty lies in determining the balance between over- and under-immunosuppression leading to graft rejection. Until recently, antiviral drugs have not been recommended for HEV infection, despite recent attempts with pegylated interferon alfa2 or ribavirine [11,15].

Conclusion

This case of HEV infection following IT confirms that HEV must now be part of the differential diagnoses considered with any case of increased liver enzymes of unexplained origin. The source of the infection does not seem to be the graft itself, but the accompanying immunosuppression, which leads to the emergence of opportunistic infections. The severe consequences of viral infection can be overcome by a progressive reduction in the level of immunosuppression, suggesting that islet graft dysfunction should always prompt etiological investigations in case an appropriate treatment might be undertaken.

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