Late Development of Diabetes mellitus after Interferon-Alfa and Ribavirin Therapy for Chronic Hepatitis C: A Case Report

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Key Words

Hepatitis C · Alfa-interferon · Immune-mediated diabetes mellitus

Abstract

Objective: To report the late development of immune-mediated diabetes mellitus after completion of alfa-interferon therapy for hepatitis C in an Asian patient. **Clinical Presentation and Intervention:** A 50-year-old male with chronic hepatitis C received treatment with alfa-interferon and ribavirin for 52 weeks. He developed immune-mediated diabetes mellitus with low C-peptide and positive antiglutamic acid decarboxylase antibody after completion of therapy. The hepatitis C infection was eradicated, but he continued to be diabetic requiring insulin therapy during the follow-up. **Conclusion:** This report shows that immune-mediated diabetes mellitus can occur as a late complication of alfa-interferon therapy.

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Introduction

It is estimated that there are some 170 million chronic hepatitis C-infected people throughout the world. Hepatitis C virus (HCV) accounts for approximately 20% of acute hepatitis, 70% with chronic hepatitis and 40% of

end-stage cirrhosis [1]. The carrier rate for HCV in Oman is about 1.2% [personal commun. from blood bank].

HCV infection of the liver has been reported to be associated with an increased prevalence of autoimmune diseases and type-2 diabetes mellitus. Treatment of chronic hepatitis due to HCV with alfa-interferon has also been reported to induce autoimmune diseases such as autoimmune hepatitis, Hashimoto's thyroiditis and immune-mediated diabetes mellitus [2]. Most reports of diabetes mellitus in this situation occur within a few months after initiation of therapy [3–5]. We report a case of chronic hepatitis C who received alfa-interferon and ribavirin treatment and later developed immune-mediated diabetes mellitus requiring insulin, after completing 52 weeks of therapy.

Case Report

A 50-year-old Asian male weighing 80 kg with a body mass index of 28 was evaluated in the Gastroenterology Clinic, The Royal Hospital, Muscat, Oman for asymptomatic elevation of liver transaminases. He denied a past history of jaundice, transfusion of blood products and had no other risk factors for acquisition of hepatitis viruses. He consumed alcohol occasionally. He was not known to be suffering from diabetes mellitus or any autoimmune disease.

Physical examination revealed that he was anicteric, not anemic, and did not have any stigmata of chronic liver disease. Abdominal examination did not reveal any hepatosplenomegaly or ascites. The laboratory parameters were as follows: Hb 16.4 g/dl,

WBC $6.2 \times 10^9/l$, platelets $240 \times 10^9/l$, prothrombin time 14.6 s, bilirubin 12 $\mu\text{mol/l}$, albumin 42 g/l, globulin 30 g/l, ALT 164 IU/l (normal <60), AST 60 IU/l (normal <40), GGT 46 IU/l, ALP 80 IU/l (normal <112), creatinine 80 $\mu\text{mol/l}$. The patient was found to be positive for HCV antibody by an ELISA test (AxSYM[®], Abbott GmbH Diagnostica, Germany). The HCV was of genotype 3 and the viral load was estimated to be 1.06 million units/ml (Amplicor, Hoffmann-La Roche Ltd., Germany). Hepatitis B virus markers were negative, as was the autoantibody profile (antinuclear factor, anti-smooth muscle antibody, LKM1 antibody). The serum ceruloplasmin and alpha-1-antitrypsin levels were within normal limits. The liver biopsy showed mild inflammation and piecemeal necrosis: grade II inflammation and stage I fibrosis (HAI scoring). The patient was started on treatment for chronic hepatitis C with alfa-interferon 3 million units (Roferon, interferon alfa-2a, Roche Pharmaceuticals, Basel, Switzerland) subcutaneously, thrice a week and ribavirin 1,200 mg/day in August 2000. At the start of therapy, random blood glucose was 6.4 mmol/l and blood glucose at 12, 24, 36 and 48 weeks was within normal range. He began to experience polydipsia and polyuria around the time of completion of the treatment at 52 weeks. The random blood sugar at this time was 18 mmol/l and he was admitted for control of hyperglycemia. The liver function tests showed normalization of ALT to 24 IU/l. HCV-RNA by PCR was negative at 24 weeks after initiation of therapy and HCV viral load was undetectable at 52 weeks. This remained undetectable for up to 24 weeks after the treatment was completed.

In October 2001, he had achieved reasonable glycemic control, but HbA1C was 12%. C-peptide was 0.3 ng/ml (normal range 0.5–4.5 ng/ml), pancreatic islet cell antibodies (ICA) <3 (normal), and antiglutamic acid decarboxylase (anti-GAD) antibody titer was 49.3 kU/l (normal less than 0.9 kU/l). The presence of anti-GAD antibody and a low C-peptide are consistent with autoimmune type-1 diabetes mellitus. The patient is currently euglycemic but requires 44 units/day of Mixtard 30HM insulin (Biphasic 30:70 human insulin suspension, Novo Nordisk A/S, Denmark). He continues to be negative for HCV RNA 10 months after completion of antiviral therapy.

Discussion

HCV infection has been linked to an increased prevalence of non-insulin-dependent diabetes mellitus (type-2 diabetes mellitus) in a number of reports [6, 7]. While the liver is important for glucose homeostasis and diabetes may occur more often in patients with HCV infection because of hepatocyte dysfunction and insulin resistance, it is also possible that autoimmune phenomena related to HCV may induce diabetes mellitus as reported in cases of autoimmune diseases such as Hashimoto's thyroiditis, glomerulonephritis, Sjögren's disease and cryoglobulinemia [8]. HCV infection results in an increased occurrence of both type-1 or type-2 diabetes.

Alfa-interferon therapy has been reported to induce multiple autoantibodies and type-1 diabetes mellitus in

patients with chronic HCV infection [3–9], but Dicesare [10] has reported that up to 13% of patients developed insulin autoantibody without the development of diabetes [10]. Most reports [3–5] described the development of insulin-dependent diabetes mellitus during the early phase of therapy with interferon-alfa for chronic hepatitis C, although the disease can present up to 4 years after completion of therapy with interferon. These patients were found to be positive for one or more multiorgan antibodies such as ICA-IgG, anti-GAD antibody, anti-insulin antibodies, anti-insulin receptor antibody and thyroid microsomal autoantibodies. HLA tissue typing demonstrates an autoimmune disease phenotype of HLA-DR 1, 3, 8-allele type.

Type-1 diabetes mellitus is regarded as a chronic autoimmune disease caused by selective destruction of the insulin-producing beta cells. The disease is mediated by T cells but autoantibodies are well-established markers for an ongoing autoimmune process within the islets. Individuals with more than one autoantibody have a higher risk of developing type-1 diabetes [11]. In the majority of previous reports [3–5] the development of antibodies and hyperglycemia occurred within a few months of starting alfa-interferon therapy. But in this patient, type-1 insulin-dependent diabetes mellitus developed around the time of completion of 52 weeks of alfa-interferon therapy. The positive anti-GAD antibodies support the autoimmune nature of the disease induced by even low-dose alfa-interferon therapy.

There is little evidence to suggest that HCV infection by itself triggers autoimmune destruction of the beta cells in the pancreatic islets. It has been shown that HCV-infected patients are hyperinsulinemic and have increased peripheral resistance to insulin, features which are compatible with type-2 non-insulin-dependent diabetes mellitus. Of the few HCV-positive diabetics who have documented insulin and beta cell autoantibodies, many have received treatment with alfa-interferon [5]. Based on these facts, we believe that the development of anti-GAD antibody-positive insulin-dependent (type-1) diabetes mellitus in this patient was induced by alfa-interferon therapy. Ribavirin is not known to induce diabetes mellitus or potentiate the effect of alfa-interferon therapy in inducing autoantibodies. There is only one other published report [12] of diabetic ketoacidosis induced by alfa-interferon and ribavirin therapy in a patient with hepatitis C and this patient also had a low C-peptide level, high anti-GAD antibody but undetectable anti-islet cell antibody [12]. Screening for autoantibodies specific for type-1 diabetes prior to initiation of alfa-interferon therapy for

chronic hepatitis C is not recommended, although some investigators believe that this should form part of the pre-therapy evaluation in patients with a family history of diabetes. Currently it is not clear how long after completion of therapy with interferon diabetes can still develop or whether patients need to be monitored for blood glucose levels on a long-term basis. We recommend that blood glucose monitoring should be an essential part of follow-up of these patients during and after completion of therapy.

Conclusion

This case shows that insulin-dependent (type-1) diabetes mellitus should be recognized as a potential side effect of combination therapy of chronic hepatitis C both during treatment and in the long term.

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