Type 1 Diabetes Mellitus with Dual Autoimmune Mechanism Related to Pegylated Interferon and Ribavirin Treatment for Chronic HCV Hepatitis

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ABSTRACT
We report a case of type 1 diabetes mellitus during pegylated interferon and ribavirin treatment for chronic hepatitis C, in a young man previously diagnosed with Hashimoto’s thyroiditis and vitiligo. The diabetes mellitus occurred during the 12th month of therapy and the cessation of interferon was necessary. Besides anti-islet autoantibodies our patient had also anti-insulin receptor autoantibodies, which explains the type B insulin resistance. One year after interferon discontinuation the patient continues insulin treatment and all the pancreatic autoantibodies are still positive. Patients with autoimmune disorders should be closely monitored and periodically tested for pancreatic autoantibodies during interferon treatment, even in the absence of hyperglycemia.

Key words: type 1 diabetes mellitus – interferon-alpha side effects – insulin resistance – hepatitis.

INTRODUCTION
Pegylated interferon and ribavirin remain mandatory in the treatment of hepatitis C virus (HCV) infected patients and a good management of peginterferon and ribavirin side effects can reduce the risk of treatment discontinuation. It is difficult to make a correlation between a rarely reported side effect and therapy. Sometimes such side effects can be life-threatening and their reporting is important for subsequent recognition of other similar cases. An increased number of reports describe autoimmune disorders related to interferon therapy, including severe cases of type 1 diabetes mellitus (T1DM). If T1DM is associated with other autoimmune disorders (thyroiditis, autoimmune gastritis, pernicious anaemia, vitiligo, coeliac disease and Addison’s disease) it can be described as the “autoimmune polyglandular syndrome” (APS) [1].

Both HCV infection and interferon treatment can be involved in the pathogenesis of diabetes mellitus (DM). HCV can be found in pancreatic beta-cells leading to a reduction of glucose-stimulated insulin release [2]. Infection with HCV usually induces type 2 DM, while alpha-interferon therapy is related to T1DM [3]. Several pancreatic associated autoantibodies (PAA) were identified: glutamic acid decarboxylase antibodies (GADAb), islet cell autoantibodies (ICA), insulinoma associated antigen 2 antibodies (IA-2 Ab), insulin autoantibodies (IAA) and zinc transporter-8 autoantibodies (ZnT8Ab). The seroconversion of GADAb was reported in 40% of patients who developed T1DM during interferon therapy [4]. There are not enough studies to define the time interval between the appearance of PAA and the
development of T1DM. Rarely, DM related to interferon therapy can be due to the development of anti-insulin receptor autoantibodies (AIRA), which produce type B insulin-resistance. Spontaneous remission is possible after interferon discontinuation [5, 6].

We report a case of T1DM related to peginterferon and ribavirin therapy for HCV chronic infection, with dual mechanism: anti-islet antibodies and type B insulin-resistance. To our knowledge this is the first case of DM with dual mechanism reported in correlation to peginterferon therapy.

CASE PRESENTATION

A 24-year old Caucasian male, with a history of vitiligo and autoimmune thyroiditis (with normal TSH, normal free-T4 - FT4 and positive anti-thyroperoxidase antibodies) was diagnosed with chronic HCV hepatitis, with a viral load (VL) of 1,850,000ui/ml and a METAVIR score at liver biopsy A2F2 (grade 2 for both necro-inflammatory activity and fibrosis). He was started on a combination treatment with peginterferon alpha 2a 180 mcg weekly and ribavirin 1000mg/day. The patient had undetectable HCV VL after 12 weeks of therapy (early virologic response). Because of the autoimmune thyroiditis the patient was monitored monthly for TSH and FT4 and also for other autoimmune disorders. After 3 months of antiviral treatment, the TSH increased, FT4 decreased and L-thyroxin therapy was started. No other autoimmune diseases were apparent at the time. Because the patient developed anemia and leukopenia after the 7th month of therapy, he was closely monitored, with weekly blood tests performed, including blood glucose. In the 12th month of therapy, without any clinical signs (neither polydipsia, nor polynuria) an increased level of blood glucose was found. The patient was admitted to hospital. His laboratory tests on admission were: fasting plasma glucose 460 mg/dL, glycated haemoglobin (HbA1c) - 8.3%, alanine aminotransferase and aspartate aminotransferase were normal, HCV VL was undetectable; he had positive anti-thyroglobulin and anti-thyroid peroxidase antibodies, normal TSH and FT4, fasting serum C-peptide level 0.2ng/mL and urinary C-peptide excretion – 9.5mg/day. The antiviral treatment was withdrawn and specific tests were performed (Table I). T1DM was diagnosed and insulin therapy was initiated.

The patient had no family history of DM and his plasma glucose level was normal before and during the first 12 months of antiviral therapy. He was not tested for PAA before starting antiviral treatment.

The patient’s human leukocyte antigen (HLA) haplotypes were DRB1*0405-DQB1*0401 and DRB1*1407-DQB1*0503. Anti-nuclear factor, anti-DNA antibodies, p ANCA, c ANCA, anti-mitochondrial antibodies, anti-Ro and anti-La antibodies were negative. The patient did not have cryoglobulinemia. Other autoimmune diseases such as: autoimmune gastritis/pernicious anemia, celiac disease, Addison’s disease, were excluded.

Severe hyperglycemia persisted in spite of high doses of insulin infusion. After one month of insulin therapy, insulin resistance was presumed, and the patient was assessed for the presence of anti-insulin receptor autoantibodies (AIRA). These autoantibodies were positive and type B insulin resistance was diagnosed. Six months after interferon therapy, the VL was undetectable (the patient had a sustained virologic response) but the blood glucose ranged from 80 to 360 mg/dL, with few episodes of hypoglycemia and with HbA1c >8%. After one year the patient is continuing with insulin therapy and both ICA and AIRA remain positive.

DISCUSSION

We present a rare side effect of pegylated-interferon therapy - T1DM. The patient was diagnosed with type 2 APS (T1DM, Hashimoto’s thyroiditis and vitiligo). Fujioka et al also presented a case of type 2 APS related to interferon treatment which associated Graves’ disease and T1DM [7]. Our patient developed a severe T1DM with dual mechanism: ICA and type B insulin resistance.

The incidence of newly onset diabetes related to interferon therapy has not been analysed in recent studies which monitored side effects. The first case of T1DM related to alpha-interferon treatment was reported by Fabris et al in 1992 [8]. In 1996, Fatovich et al and Okanoue et al appreciated that the incidence of DM related to interferon treatment was 0.08% (10 of 11241 patients) and 0.7% (5 of 677 patients) respectively [9, 10]. However, these studies did not make a clear differentiation between type 1 and type 2 DM and did not investigate PAA. The cytotoxic activity of NK and CD8+ is increased and can trigger the onset of autoimmune diseases including T1DM [11]. Interferon causes islet infiltration with T lymphocytes and monocytes and leads to pancreatic beta-cells destruction and insulin deficiency [8]. The association of ribavirin seems to enhance autoimmune disorders [12]. After the introduction of pegylated interferon, the number of patients who developed T1DM increased [13].

Although type B insulin resistance is exceptionally associated with interferon therapy, at least two cases have been reported before. Daniel et al described a 55 year-old male with HCV hepatitis who developed DM after 8 months of antiviral therapy. GADAb, IAA, IA2 Ab were negative and AIRA were positive. Two years after the discontinuation of interferon the AIRA became negative and insulin therapy was no longer necessary [6]. Another case of DM with type B

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<th>Table I. Laboratory data at the onset of T1DM</th>
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<td>Type of autoantibodies</td>
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<td>Glutamic acid decarboxylase antibodies (GAD Ab)</td>
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<td>Insulinoma associated antigen 2 antibodies (IA-2 Ab)</td>
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<td>Insulin autoantibodies (IAA)</td>
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<td>Islet cell autoantibodies (ICA)</td>
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insulin resistance related to interferon therapy was reported by Uto et al in a 57 year-old male without PAA. Two months after stopping interferon, AIRA became negative but the DM persisted [14]. In our patient, AIRA were positive one year after cessation of interferon and that could be explained by the difficulties in insulin dosage and also the episodes of hypoglycemia.

The main mechanism of T1DM related to interferon is the appearance of PAA. Fabris et al reviewed 9 studies including 440 HCV infected patients tested for PAA. Before interferon therapy 3% of the patients had positive PAA, similar to the general population, demonstrating that HCV infection does not increase the risk of pancreatic autoimmunity. During interferon therapy, the number of patients with PAA increased to 7% but only 2 patients developed T1DM (0.45%). Moreover, in this review 31 cases of T1DM related to interferon therapy were analysed. The onset of DM ranged from 10 days to 4 years after the start of the interferon [15].

Recently, Nakamura et al published the largest study on T1DM related to interferon therapy. From 1983 to 2010, 91 patients developed T1DM during or shortly after interferon therapy. Ninety-four per cent of patients had positive ICA at the onset of diabetes [16].

Nakamura et al showed that PAA appear several months before the onset of T1DM [4]. Tanaka et al reported in 2005 a case of T1DM related to peg-interferon therapy in a 51-year-old man, with negative PAA before treatment but with a significant increase in GAD antibodies titre after 24 weeks of treatment [17].

In some cases of interferon-related T1DM clinical remission was observed. This remission seems to be related to the secretion of interleukin 10 (IL-10), which suppresses the function of T helper cells and leads to the recovery of beta-cells function [18]. Another factor which seems to be correlated with remission of the disease is estrogen secretion which can preserve beta-cells function through protection from apoptosis. Estrogen can also prevent the occurrence of T1DM [19].

There is a genetic predisposition for developing T1DM. HLA haplotypes associated with a higher risk of T1DM were reported in 44-89% of patients treated with interferon [15]. The increased susceptibility seems to be linked to DRB1*0405-DQB1*0401, DRB1*0802-DQB1*0302, and DRB1*0901-DQB1*0303 [20]. One of our patient’s HLA haplotypes was DRB1*0405-DQB1*0401 which was demonstrated to be associated with T1DM induced by interferon.

It is not cost-efficient to screen all the patients treated for HCV chronic hepatitis for PAA; only a few patients had positive autoantibodies before the antiviral therapy. Moreover, these autoantibodies did not always predict the development of T1DM.

**CONCLUSION**

Patients with immune disorders who receive peg-interferon and ribavirin should be closely monitored for the occurrence of T1DM, even in the absence of hyperglycemia. It is generally accepted that antiviral therapy must be stopped immediately if T1DM occurs.

**Conflicts of interest:** The authors declare no competing interests.

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**REFERENCES**


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