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CASE REPORT

Simultaneous development of diabetic ketoacidosis and Hashitoxicosis in a patient treated with pegylated interferon-alpha for chronic hepatitis C

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Abstract

Classical interferon-alpha has been shown to be correlated with the development of a variety of autoimmune disorders. A 38 year-old female patient developed simultaneously diabetic ketoacidosis and hyperthyroidism 5 mo following initiation of treatment with pegylated interferon-α and ribavirin for chronic hepatitis C. High titers of glutamic acid decarboxylase, antinuclear and thyroid (thyroid peroxidase and thyroglobulin) antibodies were detected. Antiviral treatment was withdrawn and the patient was treated with insulin for insulin-dependent diabetes mellitus and propranolol for hyperthyroidism. Twelve months after cessation of pegylated interferon-α therapy the patient was euthyroid without any medication but remained insulin-dependent.

Key words: Autoimmune thyroiditis; Insulin dependent diabetes mellitus; Pegylated interferon-alpha; Chronic hepatitis C

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INTRODUCTION

Interferon-alpha (IFN-α), a natural protein with anti-viral, anti-proliferative and immunomodulatory effects is routinely administered in chronic hepatitis C (CHC). Classical IFN-α has been correlated with the development of a variety of autoimmune disorders including Hashimoto thyroiditis, immune-mediated thrombocytopenia, hemolytic anemia, psoriasis, rheumatoid arthritis, systemic lupus-like syndromes, primary biliary cirrhosis and sarcoidosis. The reported cumulative incidence of all autoimmune disorders ranged from 1% to 3%[1,2].

Clinical thyroid disease has been reported to develop in 10%-15% of patients treated with IFN-α for CHC[3,4]. However, it was not established whether IFN-α treatment is associated with the development of insulin dependent diabetes mellitus (IDDM). The prevalence of diabetes mellitus development in patients receiving classical IFN-α for CHC is very low ranging from 0.08% to 0.7%[1,2]. The prevalence of pancreatic auto-antibodies appeared to rise from 3% to 7% prior to and following initiation of IFN-α treatment, respectively, in a review of 9 relative studies by Fabris *et al*[5]. In those studies different types of IFN-α and variable schedules were used.

Pegylated IFN-α has been recently approved for the treatment of CHC and has been associated with only a few cases of autoimmune thyroiditis[6]. We herein describe the simultaneous development of diabetic ketoacidosis and Hashitoxicosis in a patient treated with pegylated IFN-α for CHC.

CASE REPORT

A 38-year-old female patient presented with a two fold increase of aminotransferases and positive hepatitis C virus (HCV) antibodies. HCV RNA was high (> 1 000 000 copies/mL, genotype 1b) and liver histology revealed an activity grade of 4/18 and a fibrosis score of 3/6 according to Ishak's modified HAI classification system[7]. Treatment with pegylated IFN-α-2α 180 μg/wk, in combination with oral ribavirin 1000 mg/d was initiated in February 2004. During treatment alanine aminotransferase (ALT) flares did not occur. Virological response (negative HCV RNA) was achieved at the fourth week of treatment.

In July 2004 the patient developed weakness and rapid weight loss up to 12 kg within 2 wk. Thyroid function tests revealed hyperthyroidism of autoimmune etiology, i.e. thyroid stimulating hormone (TSH): 0.008 μIU/mL (normal values: 0.15-6.1), free triiodothyronine (FT_3): 6.90 pg/mL (normal values: 2.03-4.6), free thyroxine (FT_4): 1.8 ng/dL (normal values: 0.9-1.7), positive thyroid peroxidase

(anti-TPO > 1300 IU/mL, normal values < 2 IU/mL), thyroglobulin (anti-Tg 18.6 IU/mL, normal values < 2 IU/mL) and thyroid stimulating immunoglobulin antibodies (TSI 96%, normal values: 0.02%-15%). Propranolol was administered. A few days later the patient was admitted with clinical and laboratory features indicating diabetic ketoacidosis (blood glucose: 470 mg/dl, pH: 7.08, HCO_3: 5 mmol/L). The antiviral treatment was withdrawn. Her clinical condition was improved with i.v. fluids and insulin therapy. Following normalization of the acute metabolic profile, intensive insulin therapy was recommended. The patient had no family history of diabetes mellitus. The HLA class Ⅱ typing revealed a genetic predisposition to IDDM as demonstrated by the presence of type 1 diabetes associated DRB1*03 (A*01, A*02/B*08, B*35/Cw*04, Cw*07, DRB1*03, DRB1*03/DQB1*02) haplotype (Diabetes, Pathogenesis of type 1A Diabetes In: http://www-endotext.com). Glutamic acid decarboxylase (GAD) antibodies were strongly elevated (725.52 RU/units) whereas insulin autoantibodies (IA-2) were undetectable at the onset of IDDM (< 5.3 RU/units). Additional immunological profile showed positive antinuclear antibodies (> 1:640). All the other auto-antibodies including anti-smooth muscle, anti-dsDNA, anti-ENA, anti-RNP, anti-SSA, anti-SSB, p-ANCA, c-ANCA, anti-MPO, anti-PR3, anti-LF, anti-mitochondrial were negative. The value of plasma C peptide with test glucagon was 0.61 ng/mL and 0.76 ng/mL at 0 and 6 min, respectively (normal values: 0.5-3.2 ng/mL), indicating an insulin secretion deficiency.

Twelve months after cessation of pegylated IFN-α and ribavirin therapy, the patient remained insulin dependent with a daily requirement of insulin 35 units (C-peptide levels remained low), but no medication was required for the thyroid. Last thyroid evaluation revealed a reversible condition with a decrease in the anti-TPO titers (109.5 IU/mL) and normal TSH. HCV RNA in serum was undetectable.

DISCUSSION

Classical IFN-α has been reported to induce insulin resistance[8-11] although there are also reports suggesting a beneficial effect on glucose metabolism[12-14]. However, the potential of classical IFN-α to induce IDDM has not been well established.

There have been a variety of mechanisms that may account for the effect of IFN-α on pancreatic beta cell dysfunction in patients with CHC. First, it has been reported that viral dsRNA activates the toll-like receptor-3 and the nuclear factor NFnB to induce pancreatic beta cell apoptosis and also the production of IFN-α, which is directly cytotoxic to beta cells of the pancreas. Second, IFN-α activates the oligoadenylate synthase-RnaseL pathway and the protein kinase R pathway thus inducing apoptosis of pancreatic beta cells[15]. Third, IFN-α may stimulate a counter regulatory hormone secretion (growth hormone, glucagon, etc.), thus resulting in impaired glucose tolerance[8]. Regarding IDDM, IFN-α may favour the development of Th1 immune reaction and thereby contribute to the development of autoimmune disease by the activation of CD4 lymphocytes secreting interleukin IL-2, IFN-gamma, and tumor necrosis factor[15]. IFN-α expression has also been associated with over-expression of MHC class Ⅰ antigens in human islets of pancreas[16].

Thirty five cases of IFN-α related IDDM had been reported[17-20] up to 2005. In 2003 Fabris *et al*[5] reviewed 31 cases of classical IFN-α related IDDM. A family history of IDDM was present in 3 cases and HLA haplotypes conferring susceptibility to IDDM were present in 89% of the reviewed cases. A time-period of 10 d to 4 years elapsed between the onset of treatment and the clinical development of IDDM. Fifty percent of the patients were positive for at least one pancreatic autoantibody before therapy. The rate increased to 77% during IFN-α treatment whereas 5 patients initially negative for pancreatic autoimmunity were seroconverted during therapy. Clinical manifestations included polyuria, polydipsia and weight loss in the vast majority of patients. Permanent insulin administration was required in 75% of the cases[5].

To date, the development of IDDM during pegylated IFN-α and ribavirin therapy for CHC was documented in only two cases in the English literature[21,22]. In the case reported by Jabr *et al*[21], pegylated IFN-α and ribavirin were administered in a patient with CHC and human immunodeficiency virus infection. Seven months following initiation of treatment, polyuria, generalized weakness, increased thirst and loss of appetite were manifested. Hyperosmolarity and ketoacidosis eventually developed. The patient required permanent insulin therapy thereafter. Pancreatic autoimmunity markers were not assessed. In the case presented by Cozzolongoa *et al*[22], IDDM developed following a 3-mo treatment with pegylated IFN-α-2b and ribavirin for CHC. An increase in the titers of islet-cell and glutamic acid decarboxylase antibodies before the start of therapy and 2 mo after the diagnosis of diabetes mellitus was documented. HLA class Ⅱ typing showed a predisposition to IDDM. The patient eventually required permanent insulin therapy.

Diabetic ketoacidosis was reported in a few classical IFN-α related cases[23-26], in one pegylated IFN-α related case[21] and the case herein described. The development of diabetic ketoacidosis and the permanent insulin dependency thereafter indicated a severe metabolic disturbance, which may be attributed to a rapidly developing Th1-mediated pathogenic reaction[23].

Co-existence of positive thyroid and pancreatic autoimmunity markers was documented in a few cases in the literature[23,27-29]. In the case presented by Bosi *et al*[23], clinical features of autoimmune hyperthyroidism and IDDM coexisted. In the current case the multiple autoimmune manifestations, ie. IDDM and Hashitoxicosis with highly elevated GAD and anti-TPO antibodies and additional autoimmunity markers, illustrated a vigorous triggering of the immune system by pegylated IFN-α in a genetically predisposed individual.

Gogas *et al*[30] have suggested a predictive model to identify patients with a predisposition to autoimmunity disease before the start of IFN-α therapy for melanoma. Prospective identification of the individual benefit/risk ratio would facilitate personalized treatment strategies

when IFN-α treatment is planned.

In conclusion, it seems that pegylated IFN-α shares common features with classical IFN-α as far as autoimmunity is concerned. A high clinical awareness is recommended in patients with known genetic susceptibility or positive autoimmunity markers prior to or during IFN-α therapy.

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