

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- $\alpha$  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 Antiviral treatment was withdrawn and the patient was treated with insulin for insulin-dependent diabetes mellitus and propranolol for hyperthyroidism.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- $\alpha$  therapy the patient was euthyroid without any medication but remained insulin-dependent.

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

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### INTRODUCTION

Interferon-alpha (IFN- $\alpha$ ), a natural protein with antiviral, anti-proliferative and immunomodulatory effects

is routinely administered in chronic hepatitis C (CHC). Classical IFN- $\alpha$  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%<sup>[1,2]</sup>.

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

Pegylated IFN- $\alpha$  has been recently approved for the treatment of CHC and has been associated with only a few cases of autoimmune thyroiditis<sup>[6]</sup>. We herein describe the simultaneous development of diabetic ketoacidosis and Hashitoxicosis in a patient treated with pegylated IFN- $\alpha$  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<sup>[7]</sup>. Treatment with pegylated IFN- $\alpha$ -2 $\alpha$  180  $\mu$ g/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  $\mu$ IU/mL (normal values: 0.15-6.1), free triiodothyronine (FT<sub>3</sub>): 6.90 pg/mL (normal values: 2.03-4.6), free thyroxine (FT<sub>4</sub>): 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<sub>3</sub>: 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- $\alpha$  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- $\alpha$  has been reported to induce insulin resistance<sup>[8-11]</sup> although there are also reports suggesting a beneficial effect on glucose metabolism<sup>[12-14]</sup>. However, the potential of classical IFN- $\alpha$  to induce IDDM has not been well established.

There have been a variety of mechanisms that may account for the effect of IFN- $\alpha$  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 NF $\kappa$ B to induce pancreatic beta cell apoptosis and also the production of IFN- $\alpha$ , which is directly cytotoxic to beta cells of the pancreas. Second, IFN- $\alpha$  activates the oligoadenylate synthase-RnaseL pathway and the protein kinase R pathway thus inducing apoptosis of pancreatic beta cells<sup>[15]</sup>. Third, IFN- $\alpha$  may stimulate a counter regulatory hormone secretion (growth hormone, glucagon, etc.), thus resulting in impaired glucose tolerance<sup>[8]</sup>. Regarding IDDM, IFN- $\alpha$  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<sup>[15]</sup>. IFN- $\alpha$  expression has also been associated with over-expression of MHC class I antigens in human islets of pancreas<sup>[16]</sup>.

Thirty five cases of IFN- $\alpha$  related IDDM had been reported<sup>[15,17-20]</sup> up to 2005. In 2003 Fabris *et al* reviewed 31 cases of classical IFN- $\alpha$  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- $\alpha$  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<sup>[5]</sup>.

To date, the development of IDDM during pegylated IFN- $\alpha$  and ribavirin therapy for CHC was documented in only two cases in the English literature<sup>[21,22]</sup>. In the case reported by Jabr *et al*<sup>[21]</sup>, pegylated IFN- $\alpha$  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 Cozzolongo *et al*<sup>[22]</sup>, IDDM developed following a 3-mo treatment with pegylated IFN- $\alpha$ -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- $\alpha$  related cases<sup>[23-26]</sup>, in one pegylated IFN- $\alpha$  related case<sup>[21]</sup> 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<sup>[23]</sup>.

Co-existence of positive thyroid and pancreatic autoimmunity markers was documented in a few cases in the literature<sup>[25,27-29]</sup>. In the case presented by Bosi *et al*<sup>[23]</sup>, 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- $\alpha$  in a genetically predisposed individual.

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

when IFN- $\alpha$  treatment is planned.

In conclusion, it seems that pegylated IFN- $\alpha$  shares common features with classical IFN- $\alpha$  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- $\alpha$  therapy.

## REFERENCES

- Okanoue T, Sakamoto S, Itoh Y, Minami M, Yasui K, Sakamoto M, Nishioji K, Katagishi T, Nakagawa Y, Tada H, Sawa Y, Mizuno M, Kagawa K, Kashima K. Side effects of high-dose interferon therapy for chronic hepatitis C. *J Hepatol* 1996; **25**: 283-291
- Fattovich G, Giustina G, Favarato S, Ruol A. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alpha interferon. *J Hepatol* 1996; **24**: 38-47
- Deutsch M, Dourakis S, Manesis EK, Gioustozi A, Hess G, Horsch A, Hadziyannis S. Thyroid abnormalities in chronic viral hepatitis and their relationship to interferon alfa therapy. *Hepatology* 1997; **26**: 206-210
- Mandac JC, Chaudhry S, Sherman KE, Tomer Y. The clinical and physiological spectrum of interferon-alpha induced thyroiditis: toward a new classification. *Hepatology* 2006; **43**: 661-672
- Fabris P, Floreani A, Tositti G, Vergani D, De Lalla F, Betterle C. Type 1 diabetes mellitus in patients with chronic hepatitis C before and after interferon therapy. *Aliment Pharmacol Ther* 2003; **18**: 549-558
- Maede Y, Morishita K, Iwamura K, Takayama Y, Tsukada Y, Kishino M, Shimizu T, Matsushima S, Komatsu T, Kasagi Y. Chronic hepatitis C with early complication of Grave's disease during the treatment of pegylated interferon alpha-2a. *Nippon Naika Gakkai Zasshi* 2005; **94**: 2600-2602
- Ishak K, Baptista A, Bianchi L, Callea F, De Groote J, Gudat F, Denk H, Desmet V, Korb G, MacSween RN. Histological grading and staging of chronic hepatitis. *J Hepatol* 1995; **22**: 696-699
- Koivisto VA, Pelkonen R, Cantell K. Effect of interferon on glucose tolerance and insulin sensitivity. *Diabetes* 1989; **38**: 641-647
- Ishigami Y, Kanda T, Wada M, Shimizu Y. Glucose intolerance during interferon therapy in patients with chronic hepatitis type C. *Nippon Rinsho* 1994; **52**: 1901-1904
- Imano E, Kanda T, Ishigami Y, Kubota M, Ikeda M, Matsuhisa M, Kawamori R, Yamasaki Y. Interferon induces insulin resistance in patients with chronic active hepatitis C. *J Hepatol* 1998; **28**: 189-193
- Chatterjee S. Massive increase of insulin resistance in a patient with chronic hepatitis C after treatment with interferon. *J Assoc Physicians India* 2004; **52**: 514
- Ito Y, Takeda N, Ishimori M, Akai A, Miura K, Yasuda K. Effects of long-term interferon-alpha treatment on glucose tolerance in patients with chronic hepatitis C. *J Hepatol* 1999; **31**: 215-220
- Konrad T, Zeuzem S, Vicini P, Toffolo G, Briem D, Lormann J, Herrmann G, Berger A, Kusterer K, Teuber G, Cobelli C, Usadel KH. Evaluation of factors controlling glucose tolerance in patients with HCV infection before and after 4 months therapy with interferon-alpha. *Eur J Clin Invest* 2000; **30**: 111-121
- Tai TY, Lu JY, Chen CL, Lai MY, Chen PJ, Kao JH, Lee CZ, Lee HS, Chuang LM, Jeng YM. Interferon-alpha reduces insulin resistance and beta-cell secretion in responders among patients with chronic hepatitis B and C. *J Endocrinol* 2003; **178**: 457-465
- Devendra D, Eisenbarth GS. Interferon alpha--a potential link in the pathogenesis of viral-induced type 1 diabetes and autoimmunity. *Clin Immunol* 2004; **111**: 225-233
- Foulis AK. Interferon-alpha and IDDM: comment. *Diabetologia* 1996; **39**: 127
- Sasso FC, Carbonara O, Di Micco P, Coppola L, Torella R, Niglio A. A case of autoimmune polyglandular syndrome developed after interferon-alpha therapy. *Br J Clin Pharmacol* 2003; **56**: 238-239
- Christensen UB, Krogsgaard K. Onset of type 1 diabetes mellitus during combination therapy of chronic hepatitis C with interferon-alpha and ribavirin. *Ugeskr Laeger* 2004; **166**: 1024-1025
- Schories M, Peters T, Rasenack J, Reincke M. Autoantibodies against islet cell antigens and type 1 diabetes after treatment with interferon-alpha. *Dtsch Med Wochenschr* 2004; **129**: 1120-1124
- Radhakrishnan S, Upadhyay A, Mohan N, Dhar A, Walia HK, Zubaidi G. Late development of diabetes mellitus after interferon-alfa and ribavirin therapy for chronic hepatitis C: a case report. *Med Princ Pract* 2005; **14**: 281-283
- Jabr FI, Ordinario MM. Sudden onset of diabetic ketoacidosis during pegylated interferon alfa therapy. *Am J Med* 2003; **115**: 158-159
- Cozzolongo R, Betterle C, Fabris P, Paola Albergoni M, Lanzilotta E, Manghisi OG. Onset of type 1 diabetes mellitus during peginterferon alpha-2b plus ribavirin treatment for chronic hepatitis C. *Eur J Gastroenterol Hepatol* 2006; **18**: 689-692
- Bosi E, Minelli R, Bazzigaluppi E, Salvi M. Fulminant autoimmune Type 1 diabetes during interferon-alpha therapy: a case of Th1-mediated disease? *Diabet Med* 2001; **18**: 329-332
- Bhatti A, McGarrity TJ, Gabbay R. Diabetic ketoacidosis induced by alpha interferon and ribavirin treatment in a patient with hepatitis C. *Am J Gastroenterol* 2001; **96**: 604-605
- Recasens M, Aguilera E, Ampurdanes S, Sanchez Tapias JM, Simo O, Casamitjana R, Conget I. Abrupt onset of diabetes during interferon-alpha therapy in patients with chronic hepatitis C. *Diabet Med* 2001; **18**: 764-767
- Mofredj A, Howaizi M, Grasset D, Licht H, Loison S, Devergie B, Demontis R, Cadranet JF. Diabetes mellitus during interferon therapy for chronic viral hepatitis. *Dig Dis Sci* 2002; **47**: 1649-1654
- Fabris P, Betterle C, Floreani A, Greggio NA, de Lazzari F, Naccarato R, Chiaramonte M. Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* 1992; **340**: 548
- Fabris P, Betterle C, Greggio NA, Zanchetta R, Bosi E, Biasin MR, de Lalla F. Insulin-dependent diabetes mellitus during alpha-interferon therapy for chronic viral hepatitis. *J Hepatol* 1998; **28**: 514-517
- Seifarth C, Benninger J, Bohm BO, Wiest-Ladenburger U, Hahn EG, Hensen J. Augmentation of the immune response to islet cell antigens with development of diabetes mellitus caused by interferon-alpha therapy in chronic hepatitis C. *Z Gastroenterol* 1999; **37**: 235-239
- Gogas H, Ioannovich J, Dafni U, Stavropoulou-Giokas C, Frangia K, Tsoutsos D, Panagiotou P, Polyzos A, Papadopoulos O, Stratigos A, Markopoulos C, Bafaloukos D, Pectasides D, Fountzilias G, Kirkwood JM. Prognostic significance of autoimmunity during treatment of melanoma with interferon. *N Engl J Med* 2006; **354**: 709-718

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