

Case report

Chronic hepatitis b with type I diabetes mellitus and autoimmune thyroiditis development during interferon alpha therapy

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Abstract

Interferon alpha is a molecule frequently used in the treatment of chronic hepatitis B, C, and D, with immunomodulatory and antiviral activity. It is also used in some cancer types. It has been widely claimed that interferon alpha triggers autoimmunity, with its broad adverse effect profile. Here we present the case of a 29-year-old male patient with chronic hepatitis B diagnosis who developed type I diabetes mellitus and autoimmune thyroiditis during treatment with interferon alfa-2b. Within four months of initiation of treatment with interferon alfa-2b, the patient presented to our clinic with dry mouth, urinary frequency (8 to 10 times per day), drinking plenty of water, night time urination, and tiredness. He was admitted to the clinic when his fasting blood glucose level was detected to be high. After examinations, the patient was diagnosed with type I diabetes and autoimmune thyroiditis and began to receive treatment with insulin and propranolol. Fasting blood glucose levels were controlled and thyroid hormones decreased to normal levels within one month after the treatments began. For patients who will receive treatment with interferon alpha, especially those individuals with chronic hepatitis, pancreatic autoantibodies should be checked and close monitoring should be performed as there may be glucose tolerance impairment in patients with high titers. In addition, follow-up with thyroid function tests should be performed prior to and during the treatment.

Key words: hepatitis B; interferon alpha; autoimmune thyroiditis; diabetes mellitus

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Introduction

Hepatitis B virus (HBV) is a public health problem worldwide with approximately two billion people infected; about 400 million persons are chronic carriers globally [1]. Interferon-alpha is widely used in the treatment of chronic hepatitis B and C [2]. Interferons (IFNs) are polypeptides produced by eucaryotic cells which are composed of three families containing type I IFNs (mainly IFN-alpha, IFN-beta), type II IFN (IFN-gamma), and type III IFNs. Interferon-alpha is produced by all types of leucocytes and interferon-beta is predominantly of fibroblast origin. IFN-alpha and IFN-beta are induced by virus infections [3]. Systemic side effects of interferon alpha therapy can affect various organ systems. It is an agent with immunomodulatory and antiviral effects that can be used to treat multiple myeloma, Kaposi's sarcoma, hairy cell leukemia, laryngeal papillomatosis, bladder carcinoma and renal cell carcinoma. Common adverse effects include flu-like syndrome, hematological

abnormalities, cardiovascular system symptoms, gastrointestinal symptoms (nausea, vomiting), type I diabetes mellitus, autoimmune diseases, lung dysfunction, depression and retinopathy. Interferon alpha is known to activate autoantibodies and lead to autoimmune diseases. Autoimmune diseases such as type I diabetes mellitus, thyroid diseases, psoriasis, hemolytic anemia, rheumatoid arthritis, thrombocytopenia, systemic lupus-like syndromes and sarcoidosis have been reported [4,5,6].

Type I diabetes mellitus is the result of an autoimmune condition with progressing beta-cell destruction leading to absolute insulin deficiency. The condition is characterized by leakage of T lymphocytes and monocytes to the islet and excessive release of major histocompatibility complex class-1 (MHC-class 1) antibodies. Genetic predisposition and environmental factors are required for development of autoimmune type I diabetes mellitus [7]. INF alpha may also elevate the serum level of interleukin1,

which is cytotoxic to pancreatic islet cells. The incidence of type I diabetes mellitus is very low [8].

Autoimmune thyroid diseases that develop during interferon alpha treatment occur in three ways: autoimmune primary thyroiditis, Graves' thyroiditis, and destructive thyroiditis. Thyroid disorder was detected in 4% to 14% of patients during IFN alpha therapy [9].

Here; we present a case of a male patient with chronic hepatitis B diagnosis who has developed concomitant type I diabetes mellitus and autoimmune thyroiditis during treatment with interferon alpha-2b.

Case report

A 29-year-old male patient with chronic hepatitis B diagnosis in March 2008 had been followed up for one year. During his follow-up he showed an ALT of 51 IU/ml (normal range: 5-35 IU/mL), HBV-DNA polymerase chain reaction (HBV-DNA PCR) of 25,000 copies/mL, and Knodell hepatic activity index (HAI) of 3+1+1+3=8. The patient was started on 10 million units of interferon alpha-2b treatment three times per week. The serological markers of the patient were as follows: HBsAg positive, AntiHBs negative, HBeAg negative, Anti HBe positive, AntiHCV negative, and AntiHIV negative. Anti-GAD, Anti-insulin, Anti-TPO and Anti-Tg were not tested before the treatment.

There was no abnormality in the patient's physical examination prior to the treatment except ALT elevation in his biochemical parameters. Examination results were as follows: fasting blood glucose: 101 mg/dL (Normal value: 70-105 mg/dL); urea: 17 mg/dL (N: 10-50 mg/dL); creatinine: 0.8 mg/dL (N: 0.6-1.4 mg/dL); ALT: 57 IU/mL; AST: 30 IU/mL; Alkaline Phosphatase: 80 IU/mL (N: 0-258 IU/mL); total bilirubin 0.7 mg/dL (N: 0.1-1.2 mg/dL). TSH was 1.1 IU/mL (N: 0.35-2.5); fT3: 1.85 pg/mL (N: 1.71-4.0 pg/mL); and fT4: 0.9 ng/mL (N:0.7-1.48 ng/mL) prior to the treatment. Autoantibodies antinuclear antibody (ANA), antimicrobial antibody (AMA), anti-smooth muscle antibody (ASMA) and anti-gastric parietal cell (Anti-GPC) were negative.

Within four months of the treatment, the patient presented to our clinic with dry mouth, urinary frequency (8 to 10 times per day), higher intake of water, nocturia and asthenia, and he was admitted to the clinic. His fasting blood glucose level was detected to be high (291 mg/dL). He had family history of type I diabetes mellitus (DM). His physical examination was unremarkable, except for dry lips.

Fasting blood glucose was determined to be 187 mg/dL; ALT: 23 IU/mL; AST: 18 IU/mL; urea: 14mg/dL; Na: 144 mmol/L (normal: 137-146 mmol/L); and K: 3.5 mmol/L (N: 3.5-5.2 mmol/L). Regarding complete urine analysis, density was 1010; glucose: +++++; ketone: ++; negative bilirubin; and negative protein. Serum iron and complete blood count were normal. HBV DNA was determined to be below 2,000 copies/mL by PCR. An HbA1c level of 9.6% (Normal: \leq 6%), glutamic acid decarboxylase antibody (Anti-GAD) positivity (69 U/ml – N: 0-1) and anti-insulin antibody positivity (AIA: 30.6%, N: 0-8.2%) were detected. ANA titer was determined to be 1/160. AMA, ASMA, Anti-GPC and Anti-dsDNA were negative. A low level of TSH (0.002 IU/mL), high level of fT3 and fT4 (fT3: 4.36, fT4: 2.28), anti-thyroglobulin (Anti-Tg) positivity and anti-thyroperoxidase (Anti-TPO) positivity were detected. Thyroid Doppler USG revealed a thyroid gland appearance with decreased echo compared to normal status and increased vascularisation, and Tc 99m pertechnetate thyroid scintigraphy revealed findings compatible with thyroiditis. There was no abnormal image on the pituitary MRI. The hypophysis gland was in normal dimensions, sides were even and in contrast evaluation it was homogeneously stained. An endocrinology consultation was requested for the patient. The patient was diagnosed with type I diabetes mellitus and autoimmune thyroiditis, and began to receive insulin and propranolol treatment. Fasting blood glucose levels were controlled and thyroid hormones decreased to normal levels within one month after the treatment (fT3: 1.78, fT4: 1.46). Transaminase levels were normal. Decrease in fT4 (0.40 ng/mL) and increase in TSH (57 IU/mL) were detected after three months and the patient began to receive treatment with levothyroxine. After one month, thyroid hormones, fasting blood glucose levels, and transaminase levels were normal. HBV DNA (PCR) was still below 2,000 copies/ml. In the end, the interferon treatment was discontinued at the fourth month and the patient did not receive further medication.

Discussion and conclusion

INF therapy is a treatment method that controls HBV-DNA proliferation and alleviates hepatic inflammation through immunological mechanisms or direct antiviral actions [10]. Interferon alpha therapy leads to development of several autoimmune diseases. These disorders consist of thyroid disorders (most common), systemic lupus erythematosus, and

type I diabetes mellitus [11]. Autoimmune thyroid diseases related to interferon alpha occur in three ways: autoimmune primary thyroiditis, Graves' thyroiditis, and destructive thyroiditis. Hypothyroidism is the most common adverse effect. Autoimmune thyroid disease has a multifactorial etiology. Genetic factors play a certain role. Certain drugs such as amiodaron, lithium, and sarkoidosis can be other ethiological factors. Impairment incidence in thyroid function tests as an adverse effect of interferon alpha was determined to be approximately 6% in various studies [12].

Aslan *et al.* reported a 40-year-old man with a medical history of chronic hepatitis B infection diagnosed in June 2003. He received 1.5 µg per kilogram per week of pegylated (PEG) IFN alpha-2b therapy. This was the first case report of the development of hyperthyroidy after application of PEG-IFN alpha -2b treatment. In the 32nd week of treatment, fatigue, sweating, palpitation, and sore throat symptoms were detectable in the patient. PEG-IFN alpha-2b was discontinued. Propylthiouracil (300 mg/day) and metoprolol treatment was initiated. Chronic hepatitis B infection therapy was maintained with lamivudine [13].

Marazuella *et al.* observed that TPO antibody prevalence was 14.7% in 95 patients infected with HCV (not treated with interferon alfa), very similar to the rate in the general community, and reported that the risk for thyroid dysfunction during or immediately after interferon alpha therapy in patients with positive TPO antibody increased by 3.9 fold [14].

Duncaea *et al.* reported the case of a 51-year-old man in whom IFN-alpha treatment was followed by recurrence of Gravesdisease 10 years after thyroidectomy was performed and the patient was declared cured. Despite severe thyrotoxicosis, combined IFN-alpha and ribavirin therapy was continued and radioiodine treatment was considered for Graves' disease [15].

Tran *et al.* evaluated the natural history of interferon-alpha induced thyroiditis in chronic hepatitis C patients. A cohort of 18 hepatitis C patients was taken into the study. None of the patients developed any long-term thyroid disease. Two patients had a prolonged hypothyroid phase of the thyroiditis early after the completion of treatment but recovered fully. The remaining 16 patients remained euthyroid. Similarly, thyroid autoantibodies all declined and returned to reference values [16].

The prevalence of diabetes mellitus development in patients receiving classical IFN alpha for chronic hepatitis C is very low, ranging from 0.08% to 0.7%.The prevalence of pancreatic auto-antibodies appeared to rise from 3% to 7% prior to and following initiation of IFN alpha treatment [17,18]. Fabris *et al.* presented the first case that had developed type I DM during treatment with interferon alpha for chronic hepatitis C in 1992. This patient had insulin autoantibodies before treatment and this has shown us that this patient had a predisposition for developing diabetes before treatment [19]. Fabris *et al.* also reported that in predisposed individuals, alpha-interferon can induce diabetes mellitus. The authors suggest that islet cell autoantibodies and glutamic acid decarboxylase autoantibodies should be tested before and during interferon so that patients with a high risk of developing type 1 DM can be identified [20].

Radhakrishnan *et al.* reported the late development of immune mediated diabetes mellitus after completion of alfa-interferon therapy for hepatitis C in an Asian patient. 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 the patient continued to be diabetic requiring insulin therapy during the follow-up [21].

Yamazaki *et al.* reported two cases of type I diabetes mellitus (T1DM) which developed after interferon (IFN) therapy for chronic hepatitis C. The patients had hyperglycemia with positive anti-glutamic acid decarboxylase antibodies, resulting in initiation of insulin therapy. In one case, insulin therapy could be discontinued because endogenous insulin secretion was preserved at the onset and pancreatic beta cell function was recovered thereafter. In the other case with Hashimoto's thyroiditis and Sjögren's syndrome, continuation of insulin therapy was necessary because blood glucose levels were unstably controlled. According to the authors, lasting autoimmunity superior to immunosuppressive mechanism may be associated with distinct clinical courses in these cases [22].

Soultati *et al.* reported a 38-year-old female patient developing simultaneously diabetic ketoacidosis and hyperthyroidism five months following initiation of treatment with pegylated interferon alpha and ribavirin for chronic hepatitis C.

High titers of glutamic acid decarboxylase, antinuclear and thyroid 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 [23].

Lee *et al.* reported the coexistence of type I diabetes mellitus and autoimmune thyroiditis was rarely reported. The case was a 33-year-old female patient with chronic hepatitis C who simultaneously developed diabetic ketoacidosis and autoimmune thyroiditis after treatment with pegylated interferon-alpha 2b and ribavirin [24].

Our case was a male patient who developed concomitant type I diabetes mellitus and autoimmune thyroiditis during treatment with interferon alpha-2b. The patient had normal fasting blood glucose levels and thyroid function tests before treatment with interferon alpha. ANA, AMA, ASMA and anti-GPC autoantibodies were negative. ANA titer increased to 1/160 during the treatment. Anti-GAD and Anti-insulin antibodies as well as Anti-TPO and Anti-Tg became positive and this led to the development of type I diabetes mellitus and autoimmune thyroiditis. Anti-GAD, anti-insulin, anti-TPO and anti-Tg were not tested before treatment.

For patients who will receive treatment with interferon alpha—especially those individuals with chronic hepatitis B—pancreatic autoantibodies should be checked and close monitoring must be performed as there may be glucose tolerance impairment in patients with high titers. Interruption or discontinuation of interferon alfa therapy should be considered for those patients who have increased pancreatic autoantibodies and impaired glucose tolerance during treatment [19,20,25].

Female sex, old age, and genetic predisposition are strongly related to the development of antibodies. Patients infected with hepatitis C are more prone to develop thyroid autoimmunity with interferon-alpha treatment than patients with HBV infection. Hashimoto thyroiditis is most likely to occur during the treatment and in patients with pre-existing thyroid antibodies, namely 45% to 60% compared to the 3% to 5% of those who had no circulating thyroid antibodies before interferon treatment [26].

The patients most at risk of developing either biochemical or clinical thyroid autoimmune disease during interferon a treatment are women and people

with preexisting thyroid peroxidase antibody. Patients with pre-existing thyroid peroxidase antibody tend to develop either an exacerbation of Graves' disease or Hashimoto thyroiditis during interferon treatment, while those without pre-existing antibody tend to develop thyroiditis [9,27]. There is no need to end the treatment of patients who are under control for thyroid function tests. In most cases interferon induced thyroiditis can be treated without discontinuing IFN alpha therapy, but occasionally the manifestations may be severe and require ending therapy [28].

Thyroid function and thyroid antibody should be checked before initiation of treatment and monitored during treatment.

In conclusion, interferon alpha can trigger autoimmune disorders in patients with risk factors because of its complicated effects on immune system; therefore, patients who are planning to be treated with interferon should be evaluated for autoimmune parameters both prior to and during treatment.

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