A Case of Type 1 Diabetes Onset and Recurrence of Graves’ Disease During Pegylated Interferon-Alpha Plus Ribavirin Treatment for Chronic Hepatitis C

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Abstract

We report a case of type 1 diabetes onset and recurrence of Graves’ disease during pegylated interferon (PEG-IFN)-alpha plus ribavirin treatment for chronic hepatitis C. The patient was a 55-year-old woman diagnosed with chronic hepatitis at age 46 years. She was treated for Graves’ disease at 50 years of age. Because Graves’ disease remitted, PEG-IFN-alpha plus ribavirin treatment was started for chronic hepatitis C. She was examined because of complaints of general fatigue, weight loss, and palpitations after 24 weeks of the treatment. She was diagnosed with a recurrence of Graves’ disease, and methimazole treatment was started. However, she complained of malaise, thirst, polyuria, and loss of body weight. Her fasting blood glucose level was 292 mg/dL and HbA1c was 9.3%. Serum anti-GAD (glutamic acid decarboxylase) antibodies were 2.2 U/mL. She was diagnosed with type 1 diabetes with ketosis, and insulin treatment was started. Serum anti-GAD antibodies gradually increased to 15.1 U/mL. Graves’ disease and type 1 diabetes are often complicated, and the coincidental occurrence of these 2 diseases is known as autoimmune polyglandular syndrome type III. However, only a few cases have shown that these diseases occur after IFN treatment.

Key words: Basedows’ disease, TSH receptor antibodies, HLA, autoimmune polyglandular syndrome

Introduction

Interferon (IFN) therapy is the only causal therapy used to eliminate hepatitis C virus directly when treating chronic hepatitis C (1). Recently, it has become possible to use prolonged administration and re-administration of IFN in patients with chronic hepatitis C, and IFN therapy has become popular by the introduction of pegylated interferon (PEG-IFN) and the establishment of PEG-IFN plus ribavirin combination therapy in Japan. PEG-IFN plus ribavirin combination therapy has become the mainstream therapy, and its effectiveness has improved (2). However, severe side effects of IFN therapy have been reported, including fever, arthralgia, thrombocytopenia, and leukocytopenia. IFN exerts antitumor activity, cytostatic activity and immunoregulatory effect, and antiviral activity (3). In addition, animals administered ribavirin show enhancement of autoimmune reaction (4). Thus, the combination of IFN and ribavirin may induce autoimmune-related disorders, type 1 diabetes, autoimmune thyroid disease, systemic lupus erythematosus (SLE), and rheumatoid arthritis (5-8). Graves’ disease and type 1 diabetes are considered in relation to organ-specific autoimmune disease. Here, we describe a case of new onset of type 1 diabetes and recurrence of Graves’ disease during PEG-IFN-alpha plus ribavirin treatment in a patient with chronic hepatitis C.

Case Report

A 55-year-old Japanese woman was admitted to our hospital in July 2007 complaining of symptoms including thirst,
The patient was treated with methimazole (MMI) in 2004. In 2006, her thyroid function was normalized and her TSH receptor antibodies showed a tendency to decline when PEG-IFN plus ribavirin treatment was stopped, but serum CPR was persistent at low levels and her insulin requirement was 46 units per day. Her clinical course is described in Fig. 1.

### Discussion

In the present case, new onset of type 1 diabetes and recurrence of Graves’ disease were observed following PEG-IFN-alpha plus ribavirin treatment for chronic hepatitis C. It is well known that autoimmune disorders develop following IFN treatment (5-8). IFN has been reported to exert antitumor activity, cytostatic activity and immunoregulatory effects, and antiviral activity (3). In addition, ribavirin enhances autoimmune effects in animals (4). Thus, the combination therapy of IFN and ribavirin may induce autoimmune-related disease, type 1 diabetes, autoimmune thyroid disease, and SLE (5-8). The present patient had a history of Graves’ disease; however, anti-GAD antibodies and TRAb were negative, and fasting blood glucose level was normal before PEG-IFN plus ribavirin therapy. She developed a recurrence of Graves’ disease and type 1 diabetes, and TRAb and anti-GAD antibodies were positive (at 6 and 7 months, respectively) after the commencement of PEG-IFN-alpha plus ribavirin combination therapy. Therefore, it is suspected that PEG-IFN plus ribavirin therapy may influence the development of these diseases.

It is reported that autoimmune thyroid disease is often complicated by IFN therapy, and the incidence is reported to be approximately 2-9%; the incidence of Hashimoto disease, silent thyroiditis, and Graves’ disease is 62%, 16%, and 11%, respectively (6). Thyrotoxicosis following IFN is generally transient because it is almost always associated with painless thyroiditis, and Graves’ disease is rare. In our patient, it is thought that the cause of thyrotoxicosis was
Graves’ disease, because TRAb and TSAb were positive both pre- and post treatment.

The mechanism for autoimmune thyroid disorders resulting from IFN therapy is unknown; however, several possible reasons have been suggested. One possible reason is that IFN-alpha induces overexpression of MCH class I antigens on the surface of thyroid epithelial cells (9). This overexpression is associated with the activation of cytotoxic T cells and induced destruction of thyroid tissue. IFN-alpha also causes an immune response shift to T-helper (Th) 1 predominance through the production of cytokines such as IL-2 or IFN-gamma, thereby creating predisposition to autoimmune thyroid disease (10, 11). While the mechanism for Graves’ disease after IFN therapy is unclear, it is generally known that Graves’ disease may involve Th2 dominance (12). Recently, it has been suggested that the initiation of Graves’ disease is likely mediated by Th1 lymphocytes, and this fact may be associated with the occurrence of Graves’ disease due to IFN-alpha treatment (13). On the other hand, it is reported that antithyroid antibodies are high in patients with chronic hepatitis C (7). This finding raises the possibility that hepatitis C virus infection induces an autoimmune reaction in the thyroid gland.

The frequency of newly onset diabetes following IFN therapy is reported to be 0.08-0.7% (14, 15). However, previous studies have not examined pancreatic antibodies such as anti-GAD antibody, IA-2 antibody, or ICA, thus making clear differentiation between type 1 and type 2 diabetes impossible. Thus, the frequency of newly onset type 1 diabetes following IFN therapy is uncertain. The pathogenesis of type 1 diabetes is not completely understood; however, immunologic, genetic, and environmental factors may contribute to the pathogenesis of type 1 diabetes. It is reported that IFN-alpha enhances the expression of MHC class I molecules in pancreatic beta cells, resulting in the activation of natural killer cells and T cells (16, 17). A pancreatic immuno-histochemical examination of patients with type 1 diabetes revealed that immunoreactivity IFN-alpha confined by beta cells was found in 93% of pancreatic islet cells that overexpressed MHC class I molecules (17). However, it was not found in pancreatic islet cells in nondiabetic and type 2 diabetes patients. It is reported that diabetes developed in a transgenic mouse when IFN-alpha genes were introduced into pancreatic beta cells, and that it was inhibited by the administration of anti-IFN-alpha antibodies (18). These results suggest that IFN-alpha may play an important role in the development of type 1 diabetes.

Graves’ disease and type 1 diabetes are often complicated, and the coincidental occurrence of these 2 diseases is known as autoimmune polyglandular syndrome (APS) type III (19). However, only 1 case has been reported, where Graves’ disease and type 1 diabetes developed concurrently after IFN treatment (20). In that case, it was not clear whether anti-GAD antibody and TRAb were induced by IFN because autoantibodies were not examined prior to treatment. However, in the present case, we confirmed that the anti-GAD antibody and TRAb were absent before IFN treatment and present during treatment. The mechanism of APS type III is unknown but is suspected to be strongly associated with HLA class II. Recently, it has been reported that susceptibility alleles and haplotypes of HLA class II are strongly associated with APS type III in Japanese individuals (21). In APS III patients with Graves’ disease and type 1 diabetes, the haplotype frequencies of HLA DRB1*0405-DQA1*0303-DQB1*0401, and DRB1*0802-DQA1*0301-DQB1*0302 were significantly higher than in controls. Interestingly, DNA-based typing for the HLA haplotype revealed the haplotype HLA DRB1*0405-DQA1*0303-DQB1*0401, thereby suggesting that the patient was genetically susceptible to the APS type III with Graves’ disease and type 1 diabetes. In addition, the previous case showed DRB1*0405-DQA1*0303-DQB1*0401. Given the existence...
of susceptible genes of APS type III, the combination of Graves’ disease and type 1 diabetes was not coincidental, and was likely activated by IFN-alpha plus ribavirin therapy. The present patient had HLA A-24. The destruction of beta cells in the pancreas is promoted in patients with HLA-A24 (22). Despite fasting blood glucose levels being measured at regular intervals, the patient presented with ketosis at the time of diagnosis of diabetes, and endogenous insulin secretion having been exhausted rapidly subsequently in the present case, it may be associated with HLA-A24.

In conclusion, we report here a case of new onset of type 1 diabetes and recurrence of Graves’ disease during PEG-IFN-alpha plus ribavirin treatment in a patient with chronic hepatitis C. PEG-IFN plus ribavirin combination therapy may induce autoimmune disease to a greater extent than IFN monotherapy. We recommend the regular measurement of blood glucose, thyroid hormone, and autoantibody levels, both prior to and during IFN therapy, in order to establish the occurrence of autoimmune disease.

References