Graves’ Disease Development During Sizofiran Treatment

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Abstract

It has been reported that various types of immunoactivators can induce Graves’ disease. We describe here a case of Graves’ disease during treatment with sizofiran, an immunoactivator. A 42-year-old woman who had previously been in an euthyroid state with Hashimoto’s thyroiditis, experienced thyrotoxicosis during continuous administration of sizofiran as immunotherapy for endometrial carcinoma. Since the TSH receptor-antibody was positive, and a thyroid scintigram showed diffuse goiter and high uptake, she was diagnosed as having Graves’ disease. It is suggested that the administration of sizofiran may be one of the triggers of Graves’ disease.

Case Report

The patient was a 42-year-old woman with Graves’ disease who had previously been in a euthyroid state with Hashimoto’s thyroiditis. At the age of 37 in April 1996, she had demonstrated diffuse goiter positive for anti-thyroid peroxidase-antibody (aTPO-Ab, 1:1,280) but negative for anti-thyroglobulin-antibody (aTg-Ab), and the serum concentrations of free thyroxine (FT4), free triiodothyronine (FT3) and thyroid stimulating hormone (TSH) were 1.3 ng/dl, 2.8 pg/ml and 2.0 μIU/ml, respectively. At 41 years of age in January 2000, she was diagnosed as having endometrial carcinoma. Although she had undergone a hysterectomy with bilateral adnexectomy, and received pelvic irradiation (50 Gy) and estradiol replacement therapy, serum levels of thyroid hormones were still within the normal ranges (FT4=1.1 ng/dl, FT3=2.6 pg/ml, TSH=4.1 μIU/ml) in March 2000. Thereafter, she was treated with 150 mg of nedaplatin (Shionogi Co., Osaka) six times, every month from March to July and again in November 2000, and sizofiran (Kaken Pharmaceutical Co., Tokyo), 20 mg twice a week from May to September 2000 and 40 mg twice a month from September 2000 to April 2001.

Since she noticed an increase in goiter size, she was admitted to our department on March 15, 2001. She had not consumed excess iodine in food, medicine or contrast media, and had not taken thyroid hormones. Physical examination demonstrated diffuse goiter without exophthalmos. Serum concentrations of FT4, FT3 and TSH were 2.3 ng/dl, 5.7 pg/ml and less than 0.05 μIU/ml, respectively. The serum levels of aTPO-Ab and aTg-Ab were positive (1:102,400 and 1:100, respectively), and the anti-TSH receptor-antibody (TRAb) was positive (60%). Tc-99m thyroid scintigram showed diffuse goiter and high uptake, and she was diagnosed as having Graves’ disease. Propylthiouracil has been administered to maintain serum concentrations of thyroid hormones within normal levels.

Introduction

Sizofiran is an anti-tumor polysaccharide isolated from the culture medium of Schizophyllum commune Fries. The administration of sizofiran alone or in combination with chemotherapy or radiotherapy has been found to exert tumor growth-suppressing and metastasis-suppressing effects on many types of malignancies (1–3). However, sizofiran does not exhibit any direct effect on proliferation, cellular morphology or transplantability of malignant cells, and it activates the immunological host defense system (4).

Autoimmune thyroid disease can be aggravated by many triggers. Postpartum aggravation or onset of autoimmune thyroid disease through the immune rebound mechanism is well known, and it was reported that autoimmune thyroid disease was aggravated due to an attack of allergic chinitis (5, 6). Other triggers have also been reported, for example, iodine, infection and some kinds of drugs (7–11). Interferon, amiodarone and the cessation of betamethasone activate the immune system and aggravate autoimmune thyroid disease. Sizofiran is an immunoactivator and it may aggravate autoimmune thyroid disease like these factors.

Here, we describe a case of Graves’ disease that developed during prolonged administration of sizofiran for the immunotherapy of endometrial carcinoma, and speculate that the administration of sizofiran may be one of the triggers of Graves’ disease.
Discussion

The anti-tumor activity of sizofiran is thought to be exerted via the immunological host defense system. It has been reported that sizofiran protects against bacterial infections by enhancing host immunity, and sizofiran is thought to be one of the immunomodulators that can activate the cellular and humoral immunity system (4). In fact, sizofiran has various immunological properties that modify the biological response, such as induction of natural killer cells, T-cell and macrophage activation, induction of antibody-dependent cell-mediated cytotoxicity, augmentation of complement, and increment of many cytokines (4, 12–14).

In the present case, a thyroid scintigram during thyrotoxicosis demonstrated high uptake in diffuse goiter. Moreover, there was positive TRAb, and the patient was diagnosed with Graves’ disease. She had previously been diagnosed with autoimmune thyroid disease, and Graves’ disease was induced after the administration of nedaplatin and sizofiran. Nedaplatin is an anti-tumor drug, an analog of cisplatin with lower renal toxicity (15, 16). Although many patients with cancers have received many types of anti-tumor drugs including nedaplatin or cisplatin, there is no previous report of Graves’ disease induced by these agents. However, it has been reported that many immunomodulators can influence the immune system and induce or aggravate autoimmune thyroid disease (9–11). Since sizofiran is an immunomodulator, it may be a trigger that can induce or aggravate autoimmune thyroid disease. Moreover, the onset of Graves’ disease in this case occurred during the continuous administration of sizofiran but after the cessation of nedaplatin. Therefore, we speculate that sizofiran may have been associated with the onset of Graves’ disease. However, it is also possible that nedaplatin combined with sizofiran might have induced Graves’ disease in this case, if nedaplatin modified the antigenicity of the thyroid gland with coexisting autoimmune thyroid disease. However, there has been no previous report suggesting that nedaplatin can influence thyroid autoimmunity.

Although painless thyroiditis occurs usually within several months after many triggers, the mean interval period from trigger to the onset of Graves’ thyrotoxicosis is longer than that of painless thyroiditis. Amino et al reported that painless thyroiditis was frequently aggravated from 1 to 4 months postpartum and Graves’ disease frequently developed or relapsed from 4 to 12 months postpartum (17). In most cases of interferon-triggered or amiodarone-triggered thyroid dysfunction, it had also taken longer duration before the onset of Graves’ disease than that of painless thyroiditis, and it had taken more than one year in some cases of Graves’ disease (8, 10). In the present case, thyrotoxicosis due to Graves’ disease appeared ten months after the administration of sizofiran. It may be suggested that it takes a long period from the administration of sizofiran to the appearance of Graves’ disease. However, there has not been any previous report of autoimmune disease including autoimmune thyroid disease triggered by sizofiran, and the mechanism of sizofiran-triggered thyroid dysfunction is unknown. Therefore, additional investigation into reports of autoimmune thyroid disease triggered by sizofiran will be necessary to identify which patients are at risk for this disease.

References