Clinical Case Report

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Graves disease following radioiodine therapy for toxic adenoma

Clinical case report

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Abstract

Rationale: There is a low risk of developing Graves disease (GD) with elevated thyrotropin receptor antibodies (TRAbs) in patients undergoing radioiodine therapy for toxic adenoma.

Patient concerns: An old female patient with a history of Hashimoto thyroiditis was referred to our department due to thyrotoxic symptoms. After the administration of radioiodine, a significant remission was achieved. However, after 4 months, she was referred to our department again due to recurrence of hyperthyroid symptoms.

Diagnoses: Based on the results of laboratory test, thyroid scan and ultrasound examination, she was diagnosed as thyrotoxicosis induced by toxic adenoma at the first visit. However, 4 months later, she was diagnosed as Graves' disease at the second visit.

Interventions: She received radioiodine therapy two times with different doses of 15 mCi and 12 mCi.

Outcomes: After the administration of 15 mCi radioiodine, her thyroid hormones and clinical symptoms showed significant improvement. However, 4 months later, she presented thyrotoxicosis again. After the second radioiodine therapy with a lower dose, her clinical symptoms moved towards normalization during regular follow up.

Lessons: Toxic adenoma and GD are considered as 2 distinct disease entities; however, radioiodine therapy for toxic adenoma may induce GD. We should learn to differentiate these 2 disorders prior to radioiodine therapy because of different treatment strategies and goals.

Abbreviations: FT3 = free triiodothyronine, FT4 = free thyroxine estimates, GD = Graves disease, TPOAb = thyroperoxidase antibody, TRAb = thyrotropin receptor antibody, TSH = thyroid-stimulating hormone.

Keywords: Graves disease, Hashimoto thyroiditis, radioiodine therapy, thyroperoxidase antibody, thyrotropin receptor antibodies, toxic adenoma

1. Introduction

Toxic adenoma and Graves disease (GD) are usually regarded as 2 distinct disease entities although both of them are common benign thyroid disorders. Toxic adenoma is commonly due to the overproduction of thyroid hormones by one or more autonomously functioning nodules while GD is an autoimmune disorder in which thyrotropin receptor antibodies (TRAbs) stimulate the thyroid-stimulating hormone (TSH) receptor, increasing thyroid hormone production and release.[1,2] In patients with GD, immunological examination commonly shows a transient increase of TRAb and thyroperoxidase antibodies (TPOAbs) that are undetectable in toxic adenoma.

Although radioiodine therapy is increasingly used as one of the treatment choice with safe elimination and low failure rate, the detailed treatment strategies for these 2 diseases were different with a high dose of radioiodine for toxic adenoma and low dose for GD.[1,3] For toxic adenoma, we aimed to eliminate the autonomous thyroid tissue and reestablish euthyroidism with low rate of postradioiodine hypothyroidism. With regard to GD, the thyroid tissue is usually virtually eliminated, and postradioiodine hypothyroidism is accepted with lifelong levothyroxine supplement. The dose of radioiodine and expected goal are different for toxic adenoma and GD; therefore, accurate differentiation between these 2 thyroid disorders is of prime importance.

It has been reported that several conditions, including parathyroidectomy, acute or subacute thyroiditis, and percutaneous ethanol injection, may damage follicular cells, and the released TSH-receptor antigen from damaged cells might trigger the autoimmune response which further resulted in GD.[4,5] With this similar mechanism, radioiodine therapy for autonomous thyroid disease can induce GD with temporary increase of TRAb at a very low rate of 1.3%.[1,6] Herein, we described this rare phenomenon that radioiodine therapy for toxic adenoma may induce typical GD with positive TRAb.

2. Case report

A 74-year-old woman with a long history of Hashimoto thyroiditis was referred to our department due to abnormal thyroid function. Her laboratory findings (Table 1) showed

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Table 1

Thyroid function indexes before and after the 1st and 2nd radioiodine treatment for autonomous thyroid disease.

	Normal range	Before the 1st RT	2 mo after the 1st RT	4 mo after the 1st RT/before the 2nd RT	1 mo after the 2nd RT	2 mo after the 2nd RT (100 mg levothyroxine)
TSH, mU/L	0.27–4.2	0.006 ↓	0.009 ↓	<0.005 ↓	37.29↑	12.75↑
FT3, pmol/L	3.60–7.50	14.35 ↑	4.69	8.76 ↑	2.46↓	3.12↓
FT4, pmol/L	12.0–22.0	39.70 ↑	18.34	28.15 ↑	6.70↓	19.10
TgAb, IU/mL	<115	54.98	–	29.45	–	–
TPOAb, IU/mL	<34	>600 ↑	–	>600 ↑	–	–
TRAb, IU/L	<3	1.27	–	20.89 ↑	–	–

FT3 = free triiodothyronine, FT4 = free thyroxine estimates, RT = radioiodine therapy, TgAb = antithyroglobulin antibody, TPOAb = thyroperoxidase antibody, TRAb = thyrotropin receptor antibody, TSH = thyroid-stimulating hormone.

undetectable TSH (0.006, normal range: 0.27–4.2 mU/L), elevated free triiodothyronine (FT3, 14.35, normal range: 3.60–7.50 pmol/L), free thyroxine estimates (FT4, 39.70, normal range: 12.0–22.0 pmol/L) and TPOAb (>600, normal range: <34 IU/mL), normal antithyroglobulin antibody (54.98, normal range: <115 IU/mL), and TRAb (1.27, normal range: <3 IU/L), suggesting the presence of thyrotoxicosis. In the past year, she experienced symptoms of restlessness, hyperhidrosis, and weight loss without sign of tremor or exophthalmos.

Thyroid ultrasound examination showed a $19 \times 15 \times 16$ mm solid nodule with several cystic areas in the left lobe, a 5×6 mm hypoechoic nodule in the right lobe and heterogeneous echo of extranodular thyroid. The thyroid scintigraphy of ^{99m}Tc-pertechnetate revealed a focal uptake (hot nodule) in the left lobe suppressing uptake of the extranodular thyroid tissue (Fig. 1A). The uptake of radioiodine was 29.2% and 56.7% at 3 and 24 hours, respectively. Taken together, she was diagnosed as thyrotoxicosis induced by a toxic adenoma.

Then, she received an administration of 15 mCi (millicurie) ^{131}I and was discharged without complications. Two months later, the serum levels of FT3 (4.69, normal range: 3.60–7.50 pmol/L) and FT4 (18.34, normal range: 12.0–22.0 pmol/L) moved toward normalization with a detectable decreased TSH (0.009, normal range: 0.27–4.2 mU/L), suggesting clear clinical improvement (Table 1). In addition, the hyperthyroid symptoms achieved significant remission. However, 4 months after radioiodine therapy, the patient noticed recurrence of the previous hyperthyroid symptoms. Based on the thyroid hormone results of undetectable TSH, elevated FT3, and FT4, she was suspected of hyperthyroidism recurrence (Table 1). Different from previous results, at this time, TRAb was elevated (20.89, normal range: <3 IU/L). A repeated thyroid scan showed diffuse uptake of ^{99m}Tc-pertechnetate into the thyroid without the presence of hyperfunctioning nodule that is found in the first visit (Fig. 1B). The ^{131}I uptake was still very high with 27.3% and 51.6% at 3 and 24 hours, respectively. Those 2 hypoechoic nodules were still presented in the 2nd thyroid ultrasound examination, measuring $18 \times 15 \times 12$ mm in the left lobe and $8 \times 6 \times 7$ mm in the right lobe, respectively. She was eventually diagnosed as GD, not the recurrence of autonomous thyroid disease. After an administration of lower dose ^{131}I of 12 mCi, she was discharged. During regular follow-up, slight hypothyroidism was observed and she received levothyroxine substitution.

This case report was approved by the Ethics Committee of West China Hospital of Sichuan University, Chengdu, China, and the written informed consent was obtained.

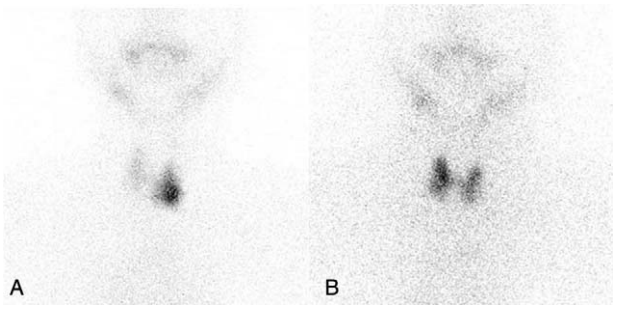

Figure 1. Thyroid scan of ^{99m}Tc-pertechnetate performed before radioiodine therapy (A), demonstrating a focal uptake (hot nodule) in the left lobe. A 2nd scan performed 4 months after radioiodine therapy (B), showing diffuse thyroid uptake without the hot nodule.

3. Discussion

This patient had a toxic adenoma in the left lobe, with long-standing Hashimoto thyroiditis, and the thyroid autoimmunity showed elevated TPOAb, normal antithyroglobulin antibody, and absent TRAb. After the first radioiodine therapy, the hot nodule was cured, but GD emerged with the appearance of TRAb and diffuse thyroid uptake of ^{99m}Tc-pertechnetate. It is reasonable that radioiodine therapy attributed to the transition of these 2 disorders.

Indeed, this phenomenon, that is the development of postradioiodine immunogenic hyperthyroidism after radioiodine therapy for autonomous thyroid disease, is usually considered rare, with the reported incidence ranging from 1% to 5%.[7–10] In the study of Schmidt, 15 of 1357 patients (1.1%) developed postradioiodine hyperthyroidism with an elevation of TRAb between 1 and 13 months after radioiodine therapy.[1] However, there was a similar shortcoming in all these studies that only a subset of included patients had measurements of autoimmune thyroid autoantibodies before or after radioiodine therapy. The potential diagnosis that the development of postradioiodine hyperthyroidism may be caused by exacerbation of preexisting GD cannot be excluded. Although it has a low prevalence of 0.8% to 2.7% among patients with GD, autonomous functioning nodules can concomitantly exist with GD, well known as Marine–Lenhart syndrome.[11] Indeed, the scintigraphic presentation of Marine–Lenhart syndrome is different from Plummer disease wherein there is more radioiodine uptake seen in the extranodular tissues.[12] In our patient, the autonomous functioning nodule significantly suppressed the uptake of

extranodular tissues. Furthermore, in such a long disease course, no elevation of TRAb was detected prior to radioiodine therapy. Taken together, the preexisting GD can be excluded.

As we know, the development of GD is related to TRAb which stimulates the TSH receptor and further increases thyroid hormone production and release. Several studies have described the development of GD following percutaneous injection of ethanol into autonomous adenomas, parathyroidectomy, surgical resection of autonomous thyroid disease, even acute, and subacute thyroiditis.[4,6,13–15] These observations favored a hypothesis that the release of TSH-receptor antigen from follicular cells damaged by radioiodine therapy might trigger an autoimmune response, further leading to GD, and this hypothesis might also apply well to our patient with postradioiodine hyperthyroidism caused by radioiodine therapy. In addition to this mechanism, it is worthy of note that our patient had a long history of Hashimoto thyroiditis, which might be a potential reason for the development of GD. Several cases were reported to develop GD with hyperthyroidism after Hashimoto thyroiditis.[16,17] The possible mechanism is that TSH receptor leakage due to damage to thyroid epithelial cells in the background of chronic lymphocytic thyroiditis, and then these antigens induce the production of anti-TSH receptor antibodies.[18] If the antibodies are predominantly stimulatory, hyperthyroidism can occur.[19] In addition, as reported in several studies, the presence of elevated pretreatment TPOAb indicated an increased risk of the development of postradioiodine GD.[1,9,20] Nygaard et al[9] reported that in patients with positive TPOAb, 6 of 27 (22%) developed Graves-like hyperthyroidism compared to 2 of 103 patients (2%) with normal TPOAb. In his another study, TRAb-associtaed hyperthyroidism after radioiodine therapy was seen in 2 of 20 patients with presence of pretreatment TPOAb compared to 1 of 129 without this antibody. A recent study even demonstrated that patients with elevated TPOAb before radioiodine therapy had a 10-fold higher risk of the development of postradioiodine immunogenic hyperthyroidism compared to those without this antibody.[1] These findings about Hashimoto thyroiditis history or pretreatment TPOAb as well as our case suggested that development of GD after radioiodine therapy might be due to an exacerbation of a possibly preexisting, occult immunogenic thyroid disorder before radioiodine therapy.[1,7]

In conclusion, severe autoimmune hyperthyroidism may occur several months after radioiodine therapy for autonomous thyroid disease, especially for those patients with Hashimoto thyroiditis history or elevated TPOAb before radioiodine therapy.

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