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Clinical report

Hyperthyroid Graves' disease after radioiodine therapy for non-toxic multinodular goiter

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Background: Radioiodine treatment has been used to reduce the size of euthyroid multinodular goiter (MNG) as an alternative to surgery. Postradioiodine Graves' disease is a rare side effect which can occur several months after radioiodine treatment for non-toxic multinodular goiter.
Objective: To report two patients who developed hyperthyroid Graves' disease after radioiodine therapy for non-toxic multinodular goiter.
Methods: We report the clinical and laboratory findings of Graves' disease which occurred after radiotherapy. The literature was reviewed for the incidence and pathogenesis of Graves' disease after radioiodine therapy.
Results: The first case describes a 39-year-old woman presented with hyperthyroidism after repeated radioiodine therapy for non-multinodular goiter. The second case describes a 45-year-old woman who presented with hyperthyroidism after the first dose of radioiodine therapy for non-multinodular goiter. Graves' disease was confirmed in both cases by the presence of thyrotropin receptor antibody (TRAb). Both patients respond well to methimazole.
Conclusion: We demonstrate the rare occurrence of Graves' disease as the side effect of radioiodine treatment for non-toxic multinodular goiter. They highlight the importance of recognizing patients with hyperthyroidism after radioiodine treatment as they could develop hyperthyroid Graves' disease following this treatment.

Keywords: Graves' disease, postradioiodine, non-toxic multinodular goiter.

Radioiodine is one treatment for patients with hyperthyroidism and thyroid cancer. However, radioiodine has recently been described as an attractive alternative to surgery in the management of benign non-toxic goiter leading to an approximate 50 % reduction in thyroid volume within 1-2 years [1]. Radioiodine is well tolerated as an outpatient procedure and can be repeated to get further reduction in volume after the first ^{131}I dose. The most well-known side effect is hypothyroidism which was estimated at occurring in about 22 % within five years [2]. Apart from hypothyroidism, postradioiodine Graves' disease was described increasingly in the past decade. In this report, we describe two patients with typical Graves' disease after radioiodine therapy for non-toxic multinodular goiter.

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Cases report

Case 1

A 39-year-old woman had noted "lumps in her neck" for 5 years. When first seen, in 2005, she denied symptoms of thyroid dysfunction. Physical examination revealed a multinodular goiter with more prominence of the left lobe. Estimated thyroid size was about 100 g by manual palpation and neck circumference was 47 cm. She also had a family history of euthyroid goiter in her sister. Thyroid function tests were consistent with euthyroidism. Thyroglobulin antibody was undetectable, while microsomal antibody was present at low titer (1/400 by hemagglutination). Thyroid ultrasonography showed an enlarged gland with a 4-cm solid nodule in the right lobe and a 5-cm solid nodule in the left lobe. Fine needle aspiration (FNA) revealed benign cytology. Surgery was advised as the first choice of treatment because of the large size of the multinodular goiter. However, she denied surgery. So ^{131}I treatment was offered as an alternative. She was treated with ^{131}I (30 mCi) in October 2005. After

^{131}I treatment, her thyroid function was checked every 3 months and levothyroxine was given at the dose of 200 μg/day to suppress her TSH level. Thyroid function tests showed euthyroidism with a suppressed level of TSH. The thyroid gland size did not change during a 1-yr follow up. Surgery was offered again to treat her large goiters but she declined again.

A second dose of ^{131}I (30 mCi) was given in Jan 2007. Levothyroxine was also given at the dose of 200 μg/day to suppress her TSH level. She complained of symptoms of hyperthyroidism 4 months after ^{131}I treatment. On physical examination, she had a heart rate of 130 beats/min, tremor in both hands, and also mild lid lag on both eyes. No exophthalmos was detected. Her thyroid function tests revealed hyperthyroidism: T3 161.4 ng/ml (Normal 58-159 ng/ml), FT4 1.95 ng/ml (Normal 0.7-1.48 ng/ml) and TSH<0.0025 μIU/ml (Normal 0.35-4.94 μIU/ml). Thyroglobulin antibody was 29.29 IU/ml (Normal 0.31-4.11 IU/ml) and Thyroid peroxidase antibody (Anti-TPO) revealed a level of more than 1,000 IU/ml (Normal 0.50-5.61 IU/ml). Graves' disease was suspected and 40 mg of methimazole was given to control her symptoms. Thyroid stimulating hormone receptor antibody (TRAb) was tested to confirm our diagnosis. TRAb test revealed a positive result with high titer at 21.8 IU/l (Normal< 1.5 IU/l by radioreceptor assay). From clinical and laboratory results, Graves' disease was confirmed in our patient. She responds well to methimazole.

Case 2

A 45-year-old woman who had a non-toxic multinodular goiter for 10 years came to our hospital in November 2006 seeking alternative treatment. She took levothyroxine 150 μg/day for 2 years but her thyroid gland remained the same size. She also had a family history of euthyroid goiter in her mother. On physical examination, the thyroid gland was estimated at about 55 g with multinodularity and neck circumference was 33.5 cm. Thyroid function tests were consistent with euthyroidism. Thyroglobulin antibody and microsomal antibody were undetectable. Thyroid ultrasonography showed diffuse enlargement of both lobes with multinodular change. ^{131}I (30 mCi) was given to reduce goiter size. Her thyroid gland reduced from 55 g to 45 g and neck circumference reduced from 33.5 cm to 31 cm in 1 month after radioiodine treatment. Levothyroxine was given at the dose of 200 micrograms per day to suppress her TSH level.

In April 2007, she started to complain of palpitation and sweating. She also lost 3 kg in 2 months. Physical examination revealed tachycardia, tremor and also a bruit in her thyroid gland. She did not have exophthalmos or lid lag. Her thyroid function tests were consistent with hyperthyroidism: T3 >800 ng/ml (Normal 58-159 ng/ml), FT4 5.57 ng/ml (Normal 0.7-1.48 ng/ml) and TSH <0.0025 μIU/ml (Normal 0.35-4.94 μIU/ml). Thyroglobulin antibody was 45 IU/ml (Normal 0.31-4.11 IU/ml) and Thyroid peroxidase antibody (Anti-TPO) was 927 IU/ml (Normal 0.50-5.61 IU/ml). Graves' disease was suspected and 30 mg of methimazole were given to control her symptoms. TRAb was done to confirm our diagnosis. The TRAb test was positive with high titer at 39.1 IU/l (Normal< 1.5 IU/l by radioreceptor assay). Her symptoms are well-controlled with methimazole.

Discussion

For more than half a century, ^{131}I therapy has been used to treat hyperthyroid disorders, primarily Graves' disease. It became evident early on that ^{131}I therapy also results in shrinkage of the thyroid gland, even if hyperthyroidism persists. Due to this effect on gland volume, ^{131}I has been used during the last two decades in the treatment of compressive nontoxic nodular goiters. However, in most countries, ^{131}I is still restricted to hyperthyroid patients. Only in a few European countries, Denmark and The Netherlands, ^{131}I is now the routine choice as treatment of the benign non-toxic multinodular goiter [3].

Radioiodine treatment in patients with non-toxic multinodular goiter is more effective in reducing the size of goiter than suppressive doses of levothyroxine, showing a goiter size reduction ranging from 40 % to 60 % within 1–2 yr of ^{131}I therapy. Although surgery is very effective and rapidly relieves pressure-related symptoms, some patients do not wish an operation, or are poor candidates for surgery. So ^{131}I therapy is increasingly being used as outpatient treatment for non-toxic multinodular goiter [1].

Late development of hyperthyroidism after ^{131}I therapy for non-toxic nodular goiter is considered uncommon. This side effect was first reported in 1995 by Nygaard *et al.* [4]. Later, the same researchers did a retrospective study in 191 patients who were treated with radioiodine [5]. Nine patients (5 %) developed hyperthyroidism 3 months after ^{131}I treatment. All hyperthyroid patients had a transient rise in serum TRAb values. This Graves'-like disease,

occurring typically within 1–6 months after treatment, is associated with the de novo appearance of TSHR antibodies, probably triggered by the release of antigenic components from follicular cells during the ^{131}I therapy [6-9]. This mechanism may be similar to the exacerbation of opthalmopathy in Graves' disease patients treated with radioiodine. This side effect must be differentiated from other causes of hyperthyroidism after radioiodine treatment, mainly radiation thyroiditis and toxic multinodular goiter. In contrast to Graves' disease, radiation thyroiditis usually occurs during the first month after treatment and manifests itself with symptoms of hyperthyroidism, neck pain, dysphagia, and also thyroid tenderness. In patients developing toxic multinodular goiter, serum TRAb values are normal, contrasted to those patients with Graves' disease. In general, the diagnosis of Graves' disease is based on the clinical presentation of the patient. However, detection of TRAbs could be used for the differential diagnosis of Graves' disease from other causes [10].

In the past, there were many case reports to describe the appearance of Graves' disease after radioiodine therapy for toxic multinodular goiter [1-14]. In a recent report, there is an estimated 1.1 % risk of developing postradioiodine Graves' disease in patients with autonomous thyroid disease [15]. Others reported incidences of postradioiodine hyperthyroidism ranging from 1 to 5 % [12, 13]. Graves' disease and toxic multinodular goiter are separate clinical entities. While Graves' disease has an autoimmune origin due to thyroid stimulating antibody (TSAb), the pathogenesis of toxic multinodular goiter are mainly attributed to non-autoimmune causes.

Our patients developed hyperthyroidism within 6 months after radioiodine treatment. Autoimmune antibodies were not detectable in them before ^{131}I treatment. But there was a considerable increase in thyroglobulin antibody and microsomal antibody after ^{131}I treatment within 4-6 months. TRAbs were not measured before administration of ^{131}I because this test is not routinely used in Thailand. Interestingly, our first patient developed this side effect after the repeated doses of ^{131}I. It is still unknown whether this complication could be related to the number of ^{131}I treatments. This patient might also have genetic susceptibility to thyroid autoimmunity, as shown by low levels of microsomal antibody in serum. This observation favors the hypothesis reported by Chiovato *et al.* [11] that, in a genetically susceptible patient, the release of TSH-receptor antigenic components from follicular cells damaged by radioiodine therapy could trigger an autoimmune process to the TSH-receptor. Indeed, Graves'disease has been reported after percutaneous injection of ethanol into toxic adenomas and following surgical resection of toxic adenoma [16-18].

Nygaard *et al.* showed that in patients with positive anti-TPO levels, 22 % developed Graves'-like hyperthyroidism compared with 2 % with normal anti-TPO levels [5]. However, the correlation between anti-TPO levels before ^{131}I treatment could be seen in patients who developed hypothyroidism after ^{131}I treatment too. In other words, the patients with high serum anti-TPO levels seem to be at risk for developing postradioiodine Graves' disease and also hypothyroidism [15]. Therefore, radioiodine treatment should be used with caution in patients with elevated anti-TPO.

Postradioiodine Graves' disease can be controlled with anti-thyroid medications for 6-18 months. One report showed that a second dose of ^{131}I treatment could produce more severe hyperthyroidism and opthalmopathy [13]. However, another report demonstrated that postradioiodine Graves' disease was treated successfully with the second dose of ^{131}I [12]. It is still a controversy whether a repeated dose of ^{131}I should be used in this condition. Our patients are well-controlled with medications only and we plan to continue anti-thyroid medications for 12 months.

In conclusion, radioiodine treatment in patients with non-toxic multinodular goiters could trigger Graves' disease in some predisposed individuals. Graves' disease can occur not only in this setting, but also in ^{131}I treatment for toxic multinodular goiter. Physicians should recognize Graves-like disease as a complication of radioiodine therapy for toxic and non-toxic multinodular goiter. They should carefully monitor in patients with possible autoimmune dispositions based on by family history and/or laboratory markers after radioiodine treatment. Information about symptoms of hyperthyroidism and regular visits in the first year after therapy are important for these patients.

The authors have no conflict of interest to declare.

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