EnM
ENDOCRINOLOGY AND METABOLISM

Case Report

Endocrinol Metab 2013;28:226-230
http://dx.doi.org/10.3803/EnM.2013.28.3.226
pISSN 2093-596X · eISSN 2093-5978

Graves' Disease that Developed Shortly after Surgery for Thyroid Cancer

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Graves' disease is an autoimmune disorder that may present with various clinical manifestations of hyperthyroidism. Patients with Graves' disease have a greater number of thyroid nodules and a higher incidence of thyroid cancer compared with patients with normal thyroid activity. However, cases in which patients are diagnosed with recurrence of Graves' disease shortly after partial thyroidectomy for thyroid cancer are very rare. Here we report a case of hyperthyroid Graves' disease that occurred after partial thyroidectomy for papillary thyroid cancer. In this case, the patient developed hyperthyroidism 9 months after right hemithyroidectomy, and antithyroglobulin autoantibody and thyroid stimulating hormone receptor stimulating autoantibody were positive. Therefore, we diagnosed Graves' disease on the basis of the laboratory test results and thyroid ultrasonography findings. The patient was treated with and maintained on antithyroid drugs. The mechanism of the recurrence of Graves' disease in this patient is still unclear. The mechanism may have been the improper response of the immune system after partial thyroidectomy. To precisely determine the mechanisms in Graves' disease after partial thyroidectomy, further studies based on a greater number of cases are needed.

Keywords: Graves' disease; Partial thyroidectomy; Thyroid cancer, papillary

INTRODUCTION

Graves' disease is an autoimmune disorder that may present with various clinical manifestations. The mechanism of development is thought to arise from thyroid stimulating hormone (TSH) receptor stimulating autoantibodies (TSHR Ab) which cause hyperthyroidism, and is accompanied by a diffuse and hypervascular goiter [1]. As a result, patients with Graves' disease have more thyroid nodules and a higher incidence of thyroid cancer compared with patients who have normal thyroid activity [2,3]. The incidence of thyroid cancer in Graves' disease patients has been reported to range from 0% to 9.8%, and papillary thyroid cancer is known to account for the majority of cases [4,5]. However cases of patients who are diagnosed with Graves' disease within a short period of time after partial thyroidectomy for thyroid cancer are very rare. Ten cases have been reported in foreign countries, but no cases have been reported in Korea [6-9]. Here we report a case of hyperthyroid Graves' disease that occurred after partial thyroidectomy for papillary thyroid cancer, together with the literature review results.

CASE REPORT

Patient: A 41-year-old female.
Main phenomena: Palpitations, heat intolerance, perspiration.
Current medical history: In November 2010, 0.5×0.6 cm

Received: 5 October 2012, **Accepted:** 12 November 2012
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hypoechoic nodules were found in the right thyroid of a female patient. Fine needle aspiration biopsy was performed. Through the pathology examination, she was diagnosed with papillary thyroid cancer and had robot thyroidectomy on the right thyroid in January 2011. During the postsurgery recovery period, she was found to have clinical features of Graves' disease, and the surgery department sent her to our department for investigation and treatment.

Past history: She had been taking antituberculous drugs since September as she had been treated for tuberculosis.

Social history: She drank two to three times a week (one bottle of Soju each time), but never smoked.

Family history: Nothing noteworthy was seen.

Scientific view: Her initial blood pressure was 133/78 mm Hg, pulse 95 beats per minute, respirations 20 breaths per minute, and body temperature 36.4°C. She had a clear level of consciousness without acute signs of disease, but She looked rather sick. The thyroid was not swollen and was painless, and there were no palpable nodules. Also, retraction of the palpebral fissures, proptosis, hyperemia of the conjunctivae, and edema were not observed.

Lab opinion: Peripheral blood was examined and the blood results were white blood cells 7,220/mm^3, hemoglobin 13.6 g/dL, hematocrit 41.2%, and platelets 353,000/mm^3, while the blood sedimentation rate was 7 mm/hr; therefore, all of the test results were normal. According to the serum biochemical examination, blood urea nitrogen was 13 mg/dL, serum creatinine 0.6 mg/dL, calcium 8.8 mg/dL, phosphorus 4.0 mg/dL, gross protein 7.0 g/dL, albumin 4.0 g/dL, aspartate aminotransferase 25 IU/L, alanine aminotransferase 34 IU/L, and gross bilirubin 0.4 mg/dL; therefore, all of the biochemical results were normal. Meanwhile, the alkaline phosphatase density was elevated (111 IU/L). According to the serum electrolyte examination, sodium density was 144 mEq/L and potassium 4.4 mEq/L.

Endocrine examination opinion: Before the operation, triiodothyronine (T3) was 80 ng/dL (normal range, 65 to 150), free thyroxine (free T4) 1.07 ng/dL (normal range, 0.89 to 1.76), and TSH 1.80 μIU/mL (normal range, 0.35 to 5.50), all of which were in the normal range, but 9 months after the operation, the patient was diagnosed with thyrotoxicosis with T3 363 ng/dL, free T4 2.33 ng/dL, and TSH 0.02 μIU/mL. Meanwhile, there was an increase in thyroglobulin (Tg) 16.6 ng/mL (normally, 1.4 to 78.0), antithyroperoxidase antibody 39.6 IU/mL (normally, 0 to 34), antithyroglobulin antibody (anti-Tg Ab) 335.8 IU/mL (normally, 0 to 60.0), and TSHR Ab 5.44 IU/L (normally, 0 to 1.75).

Image examination opinion: In the thyroid sonogram before the operation, 0.5×0.6-cm sized hypoechoic nodules were found in the right lobe of the thyroid which was a normal size, and there was no sign of increased blood flow (Fig. 1). On thyroid ultrasound after the operation, we could not find any tumor or nodule in the remaining thyroid, but the left thyroid was a little increased in size, the overall phosphorus shade reduced, and the blood flow increased (Fig. 2). However, there was no sign of enlarged cervical lymph nodes in the sonogram either before or after the operation.

Clinical course: The patient's thyroid activity examination

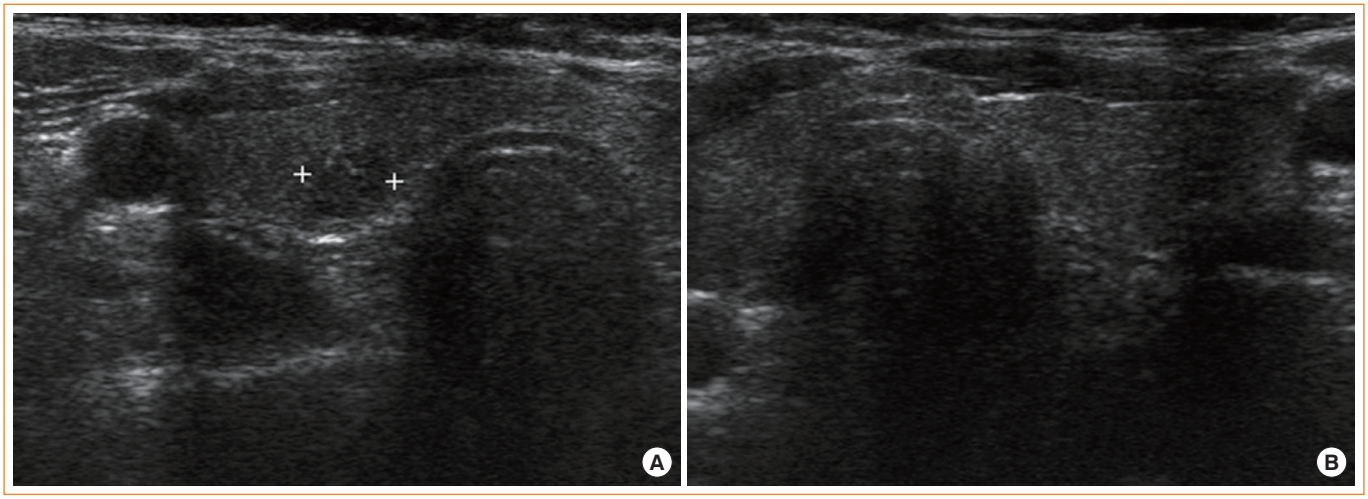

Fig. 1. Thyroid ultrasound before surgery. (A) Thyroid ultrasound shows an approximately 0.5×0.6-cm sized hypoechoic nodule in the right thyroid. (B) Ultrasound of the left thyroid shows normal findings.

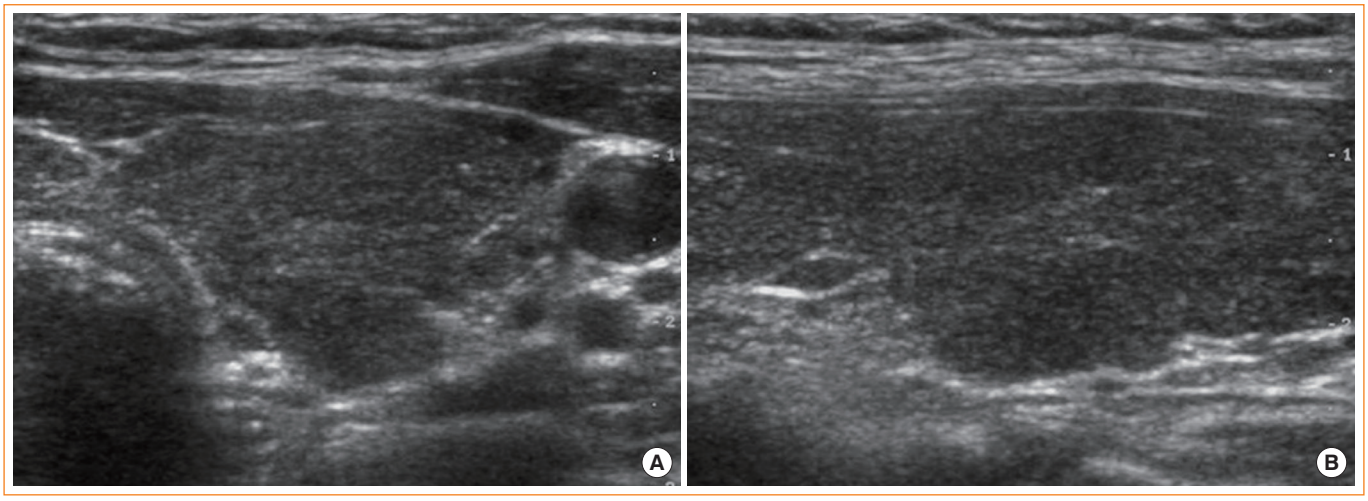

Fig. 2. Thyroid ultrasound after right partial thyroidectomy. (A) Thyroid ultrasound shows an enlarged left thyroid gland and hypoechogenicity in the transverse section. (B) In the longitudinal section, the aforementioned findings were also observed.

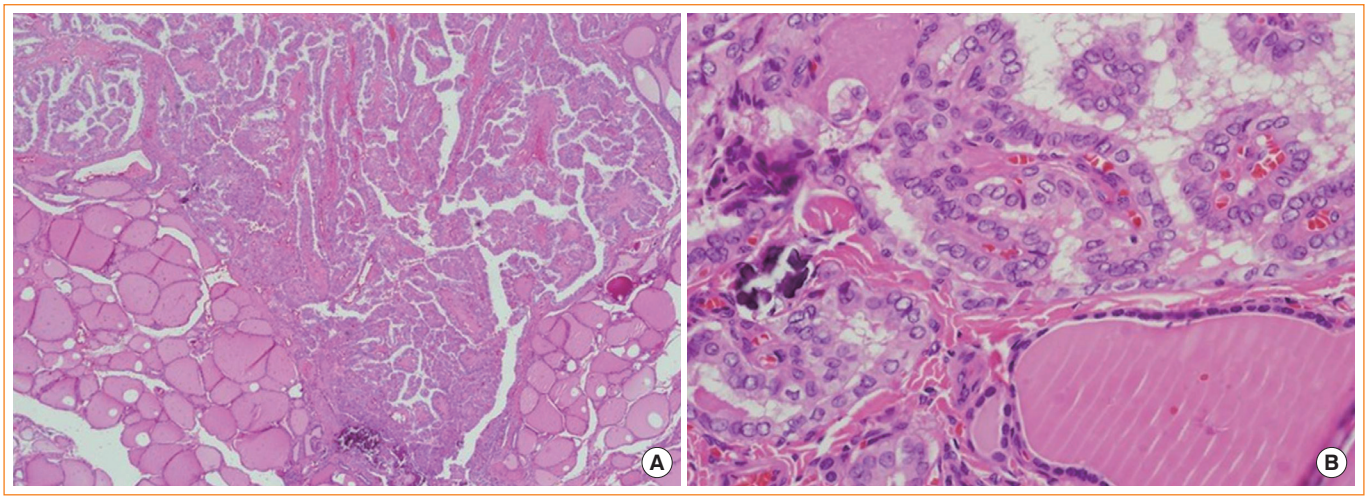

Fig. 3. Histological examination of the surgical specimen. Papillary thyroid cancer cells were seen (A, H&E stain, ×100; B, H&E stain, ×300). A papillary growth pattern is evident.

was normal 1 year before she was diagnosed with thyroid cancer and remained normal just before the thyroid cancer operation. On the preoperative thyroid ultrasound, nothing was noteworthy except for hypoechoic nodules in the right thyroid. However, she was diagnosed with thyrotoxicosis during an examination performed 3 months after the right thyroidectomy. When she was transferred to the surgery department for the operation, her T3 was 226 ng/dL, free T4 2.39 ng/dL, and TSH 0.03 μIU/mL. The surgery department decided to reduce the amount of her levothyroxine from 100 to 50 μg (Fig. 3). Since her condition had not improved at all, she stopped taking the drug, but her condition worsened 3 months later (9 months after the operation) and a blood test was performed, and eventually she was sent to the endocrinology department.

When we considered the clinical features, blood examination results, and ultrasound result, we came to the conclusion that the patient had Graves' disease resulting from the thyroid cancer operation, and we began observing the development of her disease while treating her with carbimazole 20 mg/day and propranolol 30 mg/day. After a month, follow-up tests were performed and we found that her results had greatly improved, with T3 at 177 ng/dL, free T4 1.21 ng/dL, and TSH 0.02 μIU/mL. After 6 months of drug treatment, all the values stabilized: T3 was 102 ng/dL, Free T4 1.14 ng/dL, TSH 2.02 μIU/mL, and TSHR Ab, and she currently comes to the hospital for checkups while taking carbimazole 10 mg/day.

DISCUSSION

Graves' disease is an organ-specific autoimmune disease that causes hyperthyroidism via the production of TSH receptor autoantibodies which stimulate the thyroid. Graves' disease is known to have a genetic-environmental etiology. Due to its ability to stimulate the growth of thyroid nodules, it may be accompanied by a colloid goiter, autoimmune lymphocytic disease, thyroid osteoarthritic changes, and hyperplastic adenomatous tissue [1,10]. It is common to detect Graves' disease in patients with thyroid cancer clinically, but cases of Graves' disease recurrence after partial thyroidectomy for thyroid cancer are very rare. Cases of Graves' disease occurring after thyroid operation for thyroid nodules or cancer were first described in three case reports by Tamai et al. [8] in 1982, and three more cases were reported by Misaki et al. [11] in 1997 [7]. When we looked into the seven case reports that have appeared since 1997, in four of those cases, antithyroid microsomal antibody and anti-Tg Ab were measured before the operation, and in three of those cases, antithyroid antibody tested positive. According to our analysis, all of the above seven cases took a considerable time (from 2 to 7 years) for Graves' disease to be diagnosed following thyroidectomy. In one case the disease was diagnosed 4 weeks after the operation, but the patient in that case had a thyroid that had normal function without toxic symptoms before the operation. However, antithyroid microsomal antibodies and thyroid stimulating antibodies were already elevated and a goiter was discovered on thyroid sonogram before the operation. When we looked at the time of occurrence and examination results of the cases that have been reported so far, the findings did not support the theory that thyroidectomy has a direct relationship to Graves' disease.

For the patient in the present case, although thyroid autoantibody was not measured before the operation, and there was no suspicion of thyroid autoimmune disease judging from the sonogram, blood examination, or clinical features, the patient also developed Graves' disease in a comparatively short period of time after thyroidectomy, and this case could provide good evidence that the thyroid operation itself can induce Graves' disease.

The mechanism of this phenomenon is not obvious, but some hypotheses have been presented. The first hypothesis proposes that the operation destroys thyroid cells, generating TSH receptor elevation, which causes the disease. In short, when thyroid epithelial cells are damaged during an operation, TSH receptor, Tg antigen, and microsomal antigen are secreted from the thyroid and they then stimulate the helper T cells to generate these autoantibodies, finally resulting in an increase in thyroid activity [12,13]. In contrast, the second hypothesis proposes that it is not the excessive antigens that cause the autoimmune thyroiditis, but rather an abnormality of the antigen presenting cells that keep the activation of suppressor cells or regulatory cells under control, which then attack the immune system, causing postoperative Graves' disease [14]. This theory may be supported by cases in which antibody levels were stabilized or reduced either before or after surgery in patients who already had Graves' disease [15,16]. The third hypothesis proposes that the stress from general anesthesia and surgery affects the patient physically and mentally, causing neuroendocrine fluctuations which induce immunological homeostasis [17,18]. Since the first report by Dr. Parry in 1825, there have been many reports indicating that stress is associated with Graves' disease, but the relevant mechanism has not yet been elucidated [19]. The final hypothesis is that postoperative bacterial or viral infection increases the number of $CD5^+$ B cells and these $CD5^+$ B cells stimulate the TSH receptor antibodies to provoke Graves' disease [6,20]. However, the patient in this case was not infected after the operation, and it was also unclear whether the patients in the preceding cases were infected after surgery.

In conclusion, we report our experience of the recurrence of Graves' disease possibly caused by immunological malfunctioning after partial thyroid resection. Further research is needed to establish the pathological mechanism of this disease by studying similar cases, although the condition is rare. In addition, we recommend keeping a close watch on thyroid activity both before and after partial resection for thyroid cancer or tumor.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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