NOTE

Hyperthyroid Graves’ Disease after Hemithyroidectomy for Papillary Carcinoma: Report of Three Cases

TAKASHI MISAKI, MASAHIRO IWATA, KANJI KASAGI, YASUHIRO IIDA, TAKASHI AKAMIZU*, SHINJI KOSUGI** AND JUNJI KONISHI

Department of Nuclear Medicine and Diagnostic Imaging, Kyoto University Graduate School of Medicine, Shogoin, Sakyoku, Kyoto 606-8507, Japan
* Department of Medicine and Clinical Science, Kyoto University Graduate School of Medicine, Shogoin, Sakyoku, Kyoto 606-8507, Japan
** Department of Laboratory Medicine, Kyoto University Graduate School of Medicine, Shogoin, Sakyoku, Kyoto 606-8507, Japan

Abstract. Here we report three cases of hyperthyroid Graves’ disease that occurred after partial thyroidectomy for papillary carcinoma. In Case 1, the patient first developed hyperthyroidism 2 years after resection of left thyroid lobe, was treated for 2 years with antithyroid drug which was then discontinued, and relapsed with periodic paralysis after 8 years of remission. In Case 2, a hyperfunctioning remnant thyroid was noted 22 years after right hemithyroidectomy. In Case 3, where thyrotoxic symptoms became evident 7 weeks after right hemithyroidectomy, autoantibodies to thyroglobulin and thyroid microsome were positive in preoperative serum, in line with a report by others detecting these antibodies in 2 out of 3 such cases examined. Later bioassay revealed activity of thyroid stimulating antibodies in that serum, with further increase in titer in the sample taken at the clinical manifestation. Hence in Case 3, surgical stress may have altered immunological homeostasis, promoting a preclinical Graves’ disease to full-blown hyperthyroidism.

Key words: Graves’ disease, Thyroid surgery, Thyroid cancer, TSH receptor antibodies

Past literature is rich in studies on thyroid cancer incidentally found during surgical treatment of Graves’ disease [1, 2]. However, onset of Graves’ hyperthyroidism after tumor resection has only rarely been reported [3, 4]. In the past 10 years we have experienced 3 such cases which manifested at various periods after hemithyroidectomy for papillary carcinoma, which we describe below. Of particular interest in relation to pathogenesis of Graves’ disease, in our third case, a comparison of pre- and post-surgical titers in thyroid-related autoantibodies enabled us to speculate about possible perturbation of immunoregulation by surgical procedures.

Materials and Methods

Thyroid-related indices were measured by various radioassays and immunoassays using commercially available kits; serum levels of thyroxine (T4) by SPAC T4 RIA (Daiichi Radioisotope Laboratories, Tokyo, Japan); triiodothyronine (T3) by T3 RIA-BEAD (Dinabot, Tokyo, Japan); free T4 (fT4) and free T3 (fT3) by Amerlex MAB (Ortho Clinical Diagnostics, Tokyo, Japan); TSH by RIAGNOST tTSH (CIS Diagnostics, Chiba, Japan); TSH receptor antibodies as thyrotropin binding inhibitor im-
munoglobulins (TBII) by TRAb Cosmic II (5, RSR Limited, Cardiff, United Kingdom); autoantibodies against thyroglobulin and thyroid microsome by particle agglutination, SERODIA-ATG and -AMC (TGPA and MCPA, Fuji Rebio, Tokyo, Japan); human thyroglobulin by immunoradiometric assay, Thyroglobulin-IRMA (Daiichi). We also tested activity of thyroid stimulating antibodies (TSAb) in patient sera by measuring cAMP production in FRTL5 rat thyroid cells [6].

Thyroid scintigraphy and early uptake measurement were done 30 min after intravenous injection of 148 MBq Tc-99m pertechnetate, using a Hitachi gamma camera equipped with a low-energy, high-resolution, parallel hole collimator.

### Report of the cases

#### Case 1

In 1987, a 51-year-old male visited our thyroid clinic complaining of repeated attacks of muscular weakness, recent weight loss of 2 kg, and excess sweating. Twelve years before the presentation he underwent left hemithyroidectomy for papillary carcinoma, followed by an onset of Graves’ disease 2 years later. His hyperthyroidism had been successfully treated with antithyroid drug methimazole (MMI), which had been discontinued about 2 years after the diagnosis. Blood chemistry and technetium scintigraphy confirmed relapse of Graves’ disease (Table 1 and Fig. 1). Although serum potassium was not decreased at 4.0 mEq/l, the patient was judged to have accompanying periodic paralysis, since his

#### Table 1. Thyroid indices in the 3 cases

<table>
<thead>
<tr>
<th>Case 1 (at presentation)</th>
<th>Case 2 1997/May 20</th>
<th>July/10</th>
<th>Case 3 1997/May/19 (before op) June/2 (1 wk post op) June 24 (4 wk) July 16 (7 wk)</th>
<th>reference ranges</th>
</tr>
</thead>
<tbody>
<tr>
<td>T4 (ug/dl)</td>
<td>14.4</td>
<td>*</td>
<td>12.1</td>
<td>*</td>
</tr>
<tr>
<td>rT3 (ng/dl)</td>
<td>250</td>
<td></td>
<td>165</td>
<td>*</td>
</tr>
<tr>
<td>TSH (uU/ml)</td>
<td>0.05</td>
<td></td>
<td>0.9</td>
<td>*</td>
</tr>
<tr>
<td>TBII (%)</td>
<td>29.8</td>
<td>*</td>
<td>12.7</td>
<td>*</td>
</tr>
<tr>
<td>TSAb (%)</td>
<td>*</td>
<td>457</td>
<td>507</td>
<td>*</td>
</tr>
<tr>
<td>TGPA titer</td>
<td>102400</td>
<td>*</td>
<td>100</td>
<td>*</td>
</tr>
<tr>
<td>MCPA titer</td>
<td>102400</td>
<td>*</td>
<td>1600</td>
<td>*</td>
</tr>
<tr>
<td>thyroglobulin (ng/ml)</td>
<td>&lt;1.5</td>
<td>*</td>
<td>8.4</td>
<td>*</td>
</tr>
</tbody>
</table>

a: examined at another hospital.
b: at the presentation to our institution.
*: not done.
muscular symptoms subsided after initiation of MMI therapy and potassium supplement.

Case 2

A 47-year-old hospital nurse visited our hospital complaining of mild discomfort in the anterior neck. She had right hemithyroidectomy 22 years before for papillary cancer, and had been checked up annually for thyroid function at her working place. Results on the serum taken 7 weeks before the visit already revealed chemical thyrotoxicosis (Table 1). Although she had no specific symptoms, increased pulse rate of 120 and mild finger tremor indicated sympathetic overstimulation. She was diagnosed to have Graves’ disease based on repeat blood tests (including positive TBII) and technetium scintigraphy (Table 1 and Fig. 2). Drug therapy with MMI 15 mg/day was initiated, resulting in relief of neck symptoms and normalization of thyroid function. Throughout the course, she did not have any signs of ophthalmopathy. Later, the bioassay confirmed that her serum taken at the presentation had a TSAb activity of 457%.

Case 3

A 32-year-old female had right hemithyroidectomy for papillary carcinoma. Her family history was remarkable in that her elder sister had a benign thyroid nodule. Before the surgical operation, she had been free of any thyrotoxic symptoms such as palpitation, excess sweating, general malaise, or weight loss. She did not have signs of thyroid eye disease either. Laboratory data showed decreased TSH level without elevated values of thyroid hormones (Table 1). Interestingly, preoperative neck sonography already showed diffuse goiter as well as the calcified tumor in the right lobe. At a follow-up visit 4 weeks after hemithyroidectomy, she complained of mild fever and general malaise. Seven weeks postsurgery, her thyrotoxicosis became evident with moist skin and a pulse rate of 132. In addition, mild exophthalmus with lid lag was noted. Repeat blood tests including TBII and thyroid scintigram confirmed the diagnosis of Graves’ disease (Table 1 and Fig. 3). Antithyroid drug therapy was initiated with 15 mg daily of MMI, to which the patient responded well.

Discussion

Fortunately, none of the three cases described above were free of local recurrence or of distant metastasis, which may cause thyrotoxicosis.

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**Fig. 2.** Thyroid scintigram in Case 2 at presentation. Diffusely enlarged left thyroid lobe showed homogeneously increased trapping. The thyroid uptake ratio was 1.4%.

**Fig. 3.** Thyroid scintigram in Case 3, 9 weeks after hemithyroidectomy. The remnant left thyroid lobe showed diffuse enlargement with homogeneous increase in trapping. The thyroid uptake ratio was 2.6%.
Together with the precious few reports of similar ones [3, 4], the 3 cases described above confirmed that reduction of thyroid size does not preclude thyroid hormone excess in some cases. This would be analogous to relapse of Graves' disease after subtotal thyroidectomy, and also is reminiscent of hyperthyroidism in many elderly patients with small, sometimes unpalpable thyroid. In that connection, we also observed destructive thyrotoxicosis from painless thyroiditis that occurred in another patient hemithyroidectomized for papillary cancer (unpublished). However, unlike the case reported by Umena et al. [3], no episode of precedent painless thyroiditis was noted in any of the 3 subjects with Graves' disease reported here. While the interval between surgical removal and clinical manifestation of hyperthyroidism varied widely among the three, their diagnosis is complete with diffusely increased thyroid uptake in the remnant lobe (as demonstrated in Figs. 1-3) and positive TSH receptor antibodies.

Kasuga and colleagues reported 4 cases of Graves' disease after 1680 partial thyroidectomies [4]. They found that in patients positive for TGPA and/or MCPA before surgery, the incidence of postoperative Graves' disease was 1.7% (2/117), more than ten-fold increase as opposed to 0.12% (1/795) in antibody-negative group. In our Cases 1 and 2, antibody titers were not examined preoperatively, and thyrotoxicosis occurred years after resection of the tumors, making it difficult to relate the two directly. In contrast, both antibodies were positive at the time of surgery in our Case 3, wherein thyrotoxic symptoms became evident 7 weeks after right hemithyroidectomy. Moreover, later bioassay revealed TSAb activity in that serum, with further increase in titer, together with those of the conventional thyroid autoantibodies, in the sample taken at clinical manifestation. This is in line with a previous report on 9 cases of Graves' disease examined both before and after onset of hyperthyroidism [8]. At first sight, it is tempting to speculate that in Case 3, antigen leak by surgical manipulation may boost production of antibodies to TSH receptor. However, it may not be the case, since TRAb activity has been shown to decrease or stay unchanged after thyroid operation for Graves' disease [9, 10], except for an immediate (4 hr postoperative) rise [11]. Alternatively, physical and psychological stress of general anesthesia and surgical intervention may have disturbed immunological homeostasis via neuroendocrinological pathways [12-14], promoting thyroid autoimmunity and thrusting a preclinical Graves' disease into full-blown hyperthyroidism.

In conclusion, our present experience underlined the importance of closely monitoring thyroid function after surgical removal of thyroid tumor.

References

Graves' disease: comparison with the degree of lymphocytic infiltration in the thyroid. *Autoimmunity* 8: 143–147.


