Incidental Medullary Thyroid Carcinoma in a Case of Graves’ Disease

Key words: ultrasonography, calcitonin, ret gene mutation

In 1999, Brandle et al reported two patients with Graves’ disease who had concomitant medullary thyroid carcinoma (1). The presence of medullary thyroid carcinoma was suspected in one patient who exhibited diarrhea three months after treatment with carbimazole and was detected by ultrasonography (2 cm in diameter). In the other patient, it was by Tc-99m pertechnetate scintigraphy (a 2-cm cold nodule). Here, we report a patient with Graves’ disease who had incidental medullary thyroid carcinoma.

A 32-year-old woman with Graves’ disease was referred to our hospital for further treatment in May 1996. She was diagnosed as having Graves’ hyperthyroidism in October 1994 and treatment with methimazole (MMI) was started. On physical examination, her thyroid gland was greatly enlarged and soft. Her blood pressure was 124/64 mmHg. Serum levels of free T3, free T4, and TSH were 2.4 pmol/l (normal 3.4–5.7), less than 1.3 pmol/l (normal 10.8–23.3), and 99.7 mU/l (normal 0.43–0.9), respectively, when she was on 20 mg/day of MMI. Her serum was positive for anti-TPO antibodies (37 U/ml, normal <0.3) and TSH-binding inhibitor immunoglobulins (54%, normal <15%), but negative for thyroid-stimulating antibodies (TSAb) (170%, normal <180) and anti-thyroglobulin antibodies (<0.3 U/ml, normal <0.3). Ultrasonic examination results using Aloka SSD-630 scanner with a 7.5-MHz ASU-32WL-7.5 mechanical sector probe (Aloka Co., Tokyo) showed that her thyroid gland was diffusely enlarged and did not show the presence of any nodules. The MMI dose was decreased. Then, the size of her thyroid gland decreased. Subtotal thyroidectomy was performed in August 1996 since her family doctor suggested surgical treatment. Thirty-seven grams of her thyroid gland was resected and four grams remained. A small nodular lesion without a capsule (3.5×2.5 mm2 in the section) was found in the right lobe of the resected thyroid gland. It showed solid and alveolar arrangement of small tumor cells. The cells showed fine granular cytoplasm and were immunohistochemically positive for calcitonin (Fig. 1) and carcinoembryonic antigen (CEA). Other surrounding thyroid tissue revealed diffuse hyperplasia. A diagnosis of Graves’ disease concomitant with incidental medullary thyroid carcinoma was made. Serum calcitonin and CEA levels were 110 pg/ml (normal <80) and 1.4 ng/ml (normal <2.5), respectively, before the operation when frozen serum samples were used for the measurement. She became euthyroid or subclinical hypothyroid after the operation (TSH 3.47 mU/l in April 1997 and 4.54 mU/l in December 1998). The serum calcitonin level became normal after the operation (39 pg/ml in January 1997, less than 13 pg/ml in December 1998). Ret gene mutation was not demonstrated in exons 10 (codons 609, 611, 618, and 620), 11 (codon 634), or 16 (codon 918).

When a thyroid nodule is detected in patients with Graves’ disease, the presence of thyroid carcinoma, particularly differentiated thyroid carcinoma, should be considered (2–4). TSAb are thought to play a role in promoting the growth of differentiated thyroid carcinomas having a TSH receptor on their surface (2, 5). In contrast, C-cells, the origin of medullary thyroid carcinoma cells, do not have a TSH receptor on their surface. However, it is not conclusive that the combination of medullary thyroid carcinoma and Graves’ disease is coincidental since a few reports showed that the ratio of medullary thyroid carcinoma to papillary (or follicular) thyroid carcinoma found in patients with Graves’ disease was unexpectedly high (3, 4). In our patient, the serum calcitonin level was high although the size of the tumor was very small, suggesting that measurement of the serum calcitonin level is a useful tool for diagnosing the presence of medullary thyroid carcinoma in patients with Graves’ disease even when nodular lesion is not detected by ultrasonography or scintigraphy. In addition, the serum level of calcitonin was normal (25.6±7.1 (mean±SD) pg/ml, range 13–40 pg/ml) in 24 other patients with Graves’ disease who visited our hospital in October 2001 before (n=7) and during (n=17) treatment with an anti-thyroid drug.

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Figure 1. Calcitonin immunostaining in a section of the thyroid (×20). The tumor cells are positive for calcitonin staining.
References


