Case Report

A CASE OF C-CELL HYPERPLASIA IN AN ASYMPTOMATIC V804M RET MUTATION CARRIER: CAN THE CALCIUM INFUSION TEST PREDICT C-CELL HYPERPLASIA?

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ABSTRACT

Objective: Multiple endocrine neoplasia type 2 and familial medullary thyroid carcinoma (MTC) are autosomal dominant inherited diseases caused by genetic mutations of the *RET* proto-oncogene. Prophylactic total thyroidectomy in carriers of activating *RET* proto-oncogenes, depending on mutation-based risk level, is recommended in the United States and many other countries. Measurement of calcitonin following stimulation with intravenous calcium gluconate has been widely adopted as a screening test for MTC.

Methods: Here, we describe a carrier of the *RET* V804M mutation in whom total thyroidectomy was performed at age 54 years after a calcium infusion test with the only available insurance-reimbursable calcitonin assay (an earlier generation calcitonin assay than currently reported) was employed. The case's older brother, who was also a *RET* V804M mutation carrier, was diagnosed with MTC at the age of 60 years, and his mother died of thyroid cancer with systemic metastases at the age of 76 years.

Results: During the calcium infusion test, the patient's serum calcitonin level increased from 40 to 161 pg/mL, a test result considered positive by the calcitonin assay specifications. C-cell hyperplasia, but not MTC, was noted in 2 of 11 thyroid tissue sections.

Conclusion: Although data from a more recent calcitonin assay and further information regarding the patient's mother's thyroid cancer would have been ideal, the present report adds to the literature regarding the clinical impact of the *RET* V804M mutation and the lack of specificity of older calcitonin assays for the diagnosis of MTC. **(AACE Clinical Case Rep. 2015;1:e92-e95)**

Abbreviations:
MEN = multiple endocrine neoplasia; **MTC** = medullary thyroid carcinoma; **RET** = rearranged during transfection

INTRODUCTION

Multiple endocrine neoplasia (MEN) and familial medullary thyroid carcinoma are autosomal dominant hereditary diseases caused by a mutation of the rearranged during transfection proto-oncogene (*RET*) (1,2). Medullary thyroid carcinoma (MTC) is the major prognostic sequela of this disease. The genotype-phenotype correlations of classical cysteine *RET* mutations have been the subject of several comprehensive reviews, and the association between the disease phenotype and *RET* mutation genotype may have important implications for clinical management of MEN type 2 patients and their families (3,4).

Genetic testing for *RET* mutations is now standard for MTC patients, both for diagnosis and for deciding the mode of thyroidectomy (5,6). In addition, *RET* genetic testing allows for presymptomatic prediction of MTC in *RET* mutation carriers (7). Furthermore, *RET* genetic testing provides useful information about the timing of prophylactic thyroidectomy for *RET* mutation carriers (8). Invasive MTC invariably develops in all patients with MEN2A (9). Because the tumors tend to metastasize early and the effect of medical treatment, including vandetanib, is limited, early prophylactic surgery remains the only curative option (10). Although the role of *RET* genetic testing to facilitate the identification of gene carriers for prophylactic

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surgery is not in dispute, the most appropriate timing for the operation is controversial. The prognosis is much better for those with disease confined to the thyroid gland than for those who have developed lymph node or other metastases. Ideally, surgery should be performed at the stage of C-cell hyperplasia or the early stage of MTC, before the development of invasive MTC or lymph node metastasis. Too early or overly aggressive surgical management, however, could be associated with increased surgical morbidity and is complicated by the issue of long-term drug compliance (10,11). The accumulation of the clinical phenotypes of MEN2 patients with common *RET* genotypes, such as cysteine 620 or 634, has led to evidence-based decisions regarding the optimal timing of surgery (8). Several rare *RET* mutations are reported in MEN2, however, and it is difficult to determine the optimal timing of prophylactic surgery based on such rare mutation carriers. Calcitonin stimulation tests, such as the pentagastrin or calcium infusion tests, are traditionally performed in some countries to diagnose MTC at an early stage (12,13).

Here, we describe a case of a rare *RET* mutation carrier whose thyroidectomy was done under the diagnosis of C-cell hyperplasia or early MTC by calcium infusion testing.

METHODS

Calcium Infusion Test

The calcium infusion test was performed with 2 mg/kg/min calcium gluconate. Blood samples were drawn at 1, 3, 5, and 10 min after the infusion. Serum calcitonin levels were assayed using a solid 2-site immunoradiometric assay (Mitsubishi Chemical Co, Tokyo, Japan) with polyclonal antibodies that recognized both mature calcitonin monomers and other circulating forms. According to the manufacturer, the normal range of basal serum calcitonin is 15 to 85 pg/mL. In the calcium infusion test, a ratio of peak calcitonin to basal calcitonin (P:B) greater than 3 (14) and peak stimulated calcitonin levels >100 pg/mL are defined as indicative of a significant increase.

CASE REPORT

The case was a 54-year-old man whose older brother was diagnosed at the age of 60 years with MTC and a *RET* V804M mutation. His mother died of thyroid cancer with systemic metastasis when she was 76 years old. However, no further information was available regarding her *RET* genotype or the histologic type of her thyroid tumor. No other member of his family showed any medical history or symptoms of MEN2A, such as primary hyperparathyroidism or pheochromocytoma.

Physical and endocrinologic examination, including basal calcitonin level, revealed no signs of MTC. Genetic testing revealed that he harbored the V804M mutation in *RET*. He showed an increase in calcitonin following calcium infusion (from 40 pg/mL to 161 pg/mL; P:B, 4.0), and thus, a total thyroidectomy was performed. The pathologic findings revealed C-cell hyperplasia in 2 of 11 slices of the surgically removed thyroid tissue (Fig. 1). The calcitonin level fell within the normal range following calcium infusion after surgery (from 33 pg/mL to 37 pg/mL; P:B, 1.1).

DISCUSSION

In the present case, although the basal calcitonin level remained within normal range, it increased following a calcium infusion test before surgery. Pathologic examination revealed C-cell hyperplasia in only 2 of 11 specimen slices. In contrast, calcitonin elevation after calcium infusion testing has been reported in non-MTC lesions (15). In addition, C-cell hyperplasia occurs in a proportion of normal subjects (16,17). C-cell hyperplasia has been divided into physiologic and neoplastic types. Physiologic hyperplasia has been described in association with a great variety of

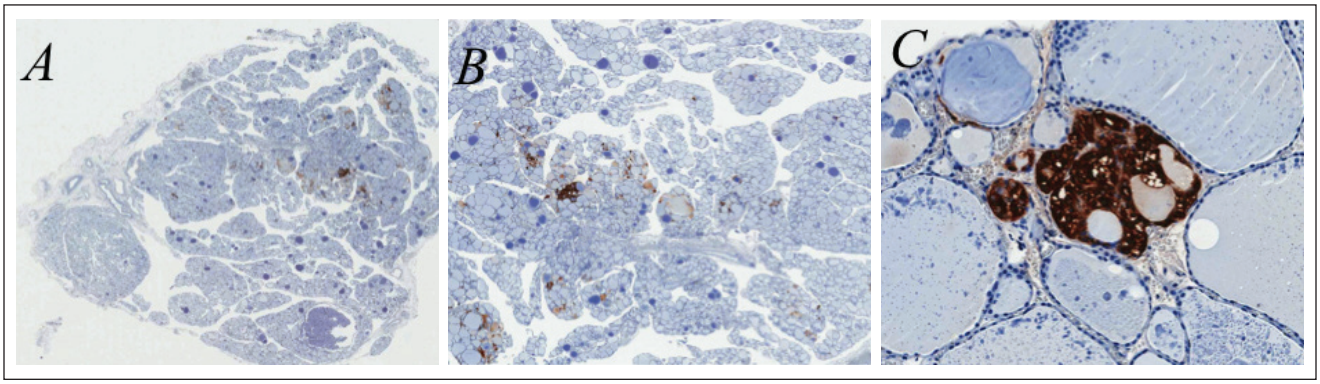

Fig. 1. C-cell hyperplasia: histologically, C-cell hyperplasia was observed in 2 of 11 slices. (*A*) Physiologic C-cell hyperplasia showing increased numbers of calcitonin-positive C cells (macro image). (*B*) Immunohistochemical staining with anti-calcitonin antibody showed more than 50 C cells per low-power (10×) field. (*C*) More than 6 C cells per thyroid follicle were detected (×100).

conditions, including aging, hyperparathyroidism, hypergastrinemia, Hashimoto's thyroiditis, non-Hodgkin's lymphoma, and follicular tumors. It is difficult to distinguish between physiologic and neoplastic hyperplasia using the calcium infusion test. Recently, Lorenz et al (18) reported significant increases in calcitonin levels after calcium stimulation in non–C-cell disease patients. However, as in the present case, C-cell hyperplasia can be detected in restricted regions in the thyroid gland (19). Therefore, routine histopathologic examination might miss the C-cell hyperplasia lesions. In addition, as the basal level of calcitonin in the Lorenz et al report was lower than in the present calcitonin assay, the calculated P:B calcitonin ratio should be higher than that of our assay. We speculate that non-MTC patients who exhibit increased calcitonin levels following a calcium infusion test might have C-cell hyperplasia somewhere in the thyroid gland, although it is not pathogenic (20).

Calcitonin levels were determined in the present study using an immunoradiometric assay with polyclonal antibodies that recognize various forms of calcitonin, such as polymer forms, as this was the only clinical assay kit for calcitonin available in Japan. A sandwich method such as chemiluminescent enzyme immunoassay or radioimmunoassay using a monoclonal antibody measure only the monomer form of calcitonin.

The patient and family history should help in this distinction. Considering the background of *RET* mutation, elevated calcitonin following the calcium infusion test suggests the presence of neoplastic C-cell hyperplasia. Although physiologic hyperplasia does not require treatment, we believe that C-cell hyperplasia in *RET* mutation carriers should be managed by total thyroidectomy, such as in the present case.

CONCLUSION

Although further studies are required to provide hard evidence regarding the optimal timing of total thyroidectomy, the present case suggests that calcium infusion testing may be useful for determining the optimal timing for total thyroidectomy in patients who are carriers of rare, less invasive *RET* mutations.

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DISCLOSURE

The authors have no multiplicity of interest to disclose.

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