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DIFFICULT CASE

A Case of Multiple Endocrine Neoplasia Type 2B Undiagnosed for Many Years Despite its Typical Phenotype

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We report the case of a 24-yr-old man with a typical phenotype of multiple endocrine neoplasia type 2B (MEN 2B). The patient had previously undergone minor surgery to remove multiple tumors on the lip, but he had no further examinations. MEN 2B was suspected owing to characteristic multiple ganglioneuromatosis when the patient presented with a goiter associated with high levels of plasma calcitonin and CEA. Aspiration biopsy cytology revealed medullary thyroid carcinoma (MTC), and abdominal computed tomography and nuclear scanning with metaiodobenzylguanidine revealed bilateral adrenomedullary tumors. Adrenomedullary function tests showed high levels of serum and urinary fractionated catecholamines, and genetic analysis showed a point mutation in the codon 918 (M918T) of the RET gene. The patient was diagnosed with MEN 2B and underwent right adrenalectomy and total thyroidectomy. No distant metastasis of the MTC was noted although MEN 2B had remained undiagnosed since the ganglioneuromatosis was first noticed. MEN 2B is a rare hereditary disorder, but the occurrence of characteristic ganglioneuromatosis was quite helpful in making the diagnosis.

Key Words: Multiple endocrine neoplasia type 2B; mutation; ganglioneuromatosis; pheochromocytoma; medullary thyroid carcinoma.

Introduction

The autosomal dominantly inherited multiple endocrine neoplasia type 2 (MEN 2) syndrome is subdivided into MEN 2A, MEN 2B, and familial medullary thyroid carcinoma (FMTC). MEN 2A is characterized by MTC, pheochromocytoma, and hyperparathyroidism. MEN 2B is similar to MEN 2A except that hyperparathyroidism is absent, and that the characteristic developmental abnormalities, such as marfanoid habituation and ganglioneuromatosis, are present. In FMTC, MTC is the only phenotype of the disease. The ganglioneuromatosis appears on the conjunctiva, tongue, and lip and thus are easily noticed and quite helpful in making a diagnosis in MEN 2B, especially in determining a proband. Once a proband is found, both biochemical and genetic analyses are used for family screening.

It is well established that germline mutations of the RET protooncogene play a crucial role in the pathogenesis of MEN 2 and that there are several hot spots of RET mutations; in MEN 2A, the cysteine-rich domain is targeted, and in MEN 2B,the tyrosine kinase domain is targeted. Nearly all cases of MEN 2B have a single point mutation in the codon 918 resulting in the substitution of methionine for threonine, which lies intracellular within the catalytic core of the tyrosine kinase domain. Clinically useful direct DNA tests are now available to identify gene carriers before any clinical or biochemical abnormality occurs, and since MTC is particularly aggressive in patients with MEN 2B, early diagnosis and surgical treatment are very important. We describe herein a Japanese patient with MEN 2B who was undiagnosed for more than about 10 yr despite its typical phenotype.

Case Study

A 24-yr-old man was referred to our hospital because of a goiter and multiple ganglioneuromatosis. When he was a junior high school student, he had undergone surgery to remove multiple tumors on the lip, but he had no further examination. On present examination, multiple ganglioneuromatosis on the conjunctiva, tongue, and lip were noted (Fig. 1), and he showed a marfanoid body habitus. The patient had no headache, sweating, palpitations, or hypertensive episodes. Blood chemistry tests including serum calcium were normal and parathyroid hormone (PTH) level was within the normal range. A goiter associated with high levels of calcitonin and CEA (Table 1) was noted, and computed tomography (CT) and ultrasonography of the thyroid showed a multiple mass in the bilateral lobe (Fig. 2). Aspiration biopsy cytology revealed an MTC. Abdominal CT disclosed bilateral adrenal tumors, and nuclear scanning with metaiodobenzylguanidine (^{131}I-MIBG) showed its accumulation in the bilateral adrenal tumors in addition to uptake

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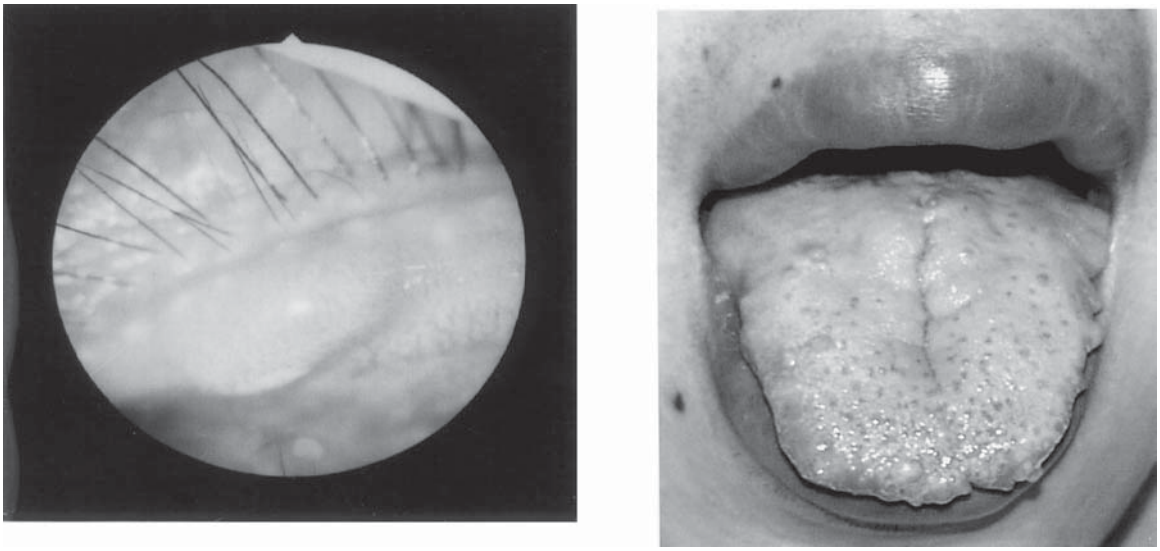


Fig 1. Multiple ganglioneuromatosis can be observed on (**A**) the conjunctiva and (**B**) tongue.

Table 1
Endocrinologic Test Results

Test	Units	
Serum epinephrine	167 pg/mL	(<100)
Serum norepinephrine	296 pg/mL	(100–450)
Serum dopamin	13 pg/mL	(<20)
Urinary epinephrine	135.5 μg/d	(3.0–15.0)
Urinary norepinephrine	139.9 μg/d	(26.0–121.0)
Urinary dopamin	926.6 μg/d	(190–720)
Urinary metapinephrine	4.25 mg/d	(0.05–0.23)
Urinary normetanepine	0.63 mg/d	(0.07–0.26)
Urinary VMA	4.25mg/d	(1.3–5.1)
Thyroid-stimulating hormone	17.7 μIU/mL	(0.34–3.50)
fT_4	1.61 ng/dL	(0.90–1.80)
fT_3	3.80 pg/mL	(2.50–4.50)
Calcitonin	2020 pg/mL	(15–86)
CEA	17.1 ng/mL	(0.0–2.5)
Intact PTH	14.2 pg/mL	(10.0–65.0)

in the thyroid gland (Fig. 3). Laboratory tests revealed high levels of serum and urinary fractionated catecholamines and their metabolites (Table 1). Genomic DNA was extracted from the patient's peripheral blood after obtaining informed consent. Polymerase chain reaction–based direct sequencing was performed as described previously *(1)*. A heterozygous germline mutation was identified on codon 918 in the RET gene (Fig. 4). The patient was diagnosed as having MEN 2B as characterized by MTC, pheochromocytoma, and ganglioneuromatosis. Initially, he underwent right adrenalectomy after his blood pressure was controlled with

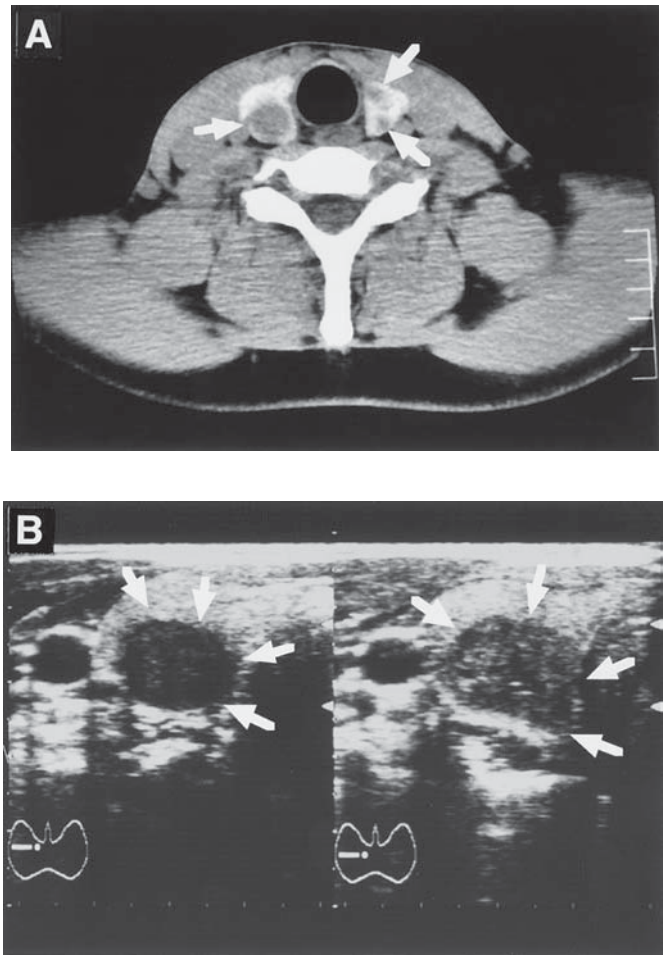
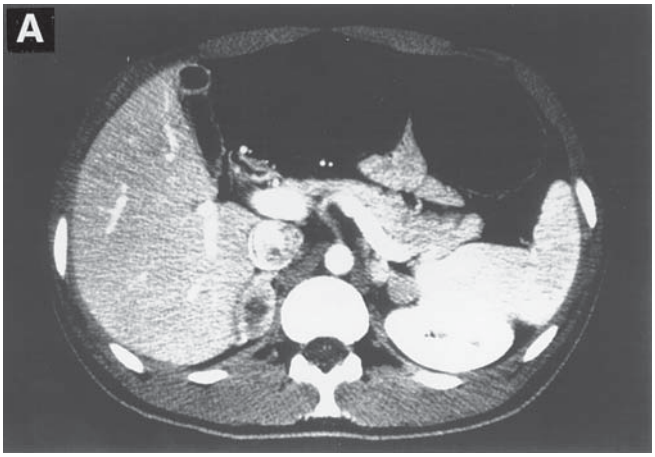


Fig. 2. (**A**) Axial CT image of the neck showing multiple thyroid tumor; (**B**) ultrasonographic image of thyroid showing a multiple hypoechoic mass with microcalcification.



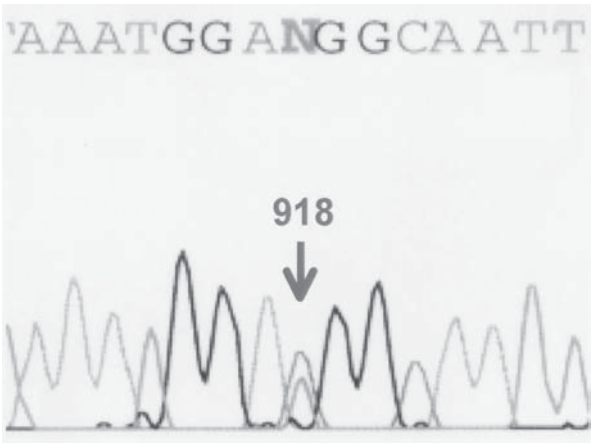


Fig. 4. RET gene point mutation in germline DNA from an MEN 2B patient. This patient had one normal allele and a mutant allele with a T → C change at codon 918 (arrow).

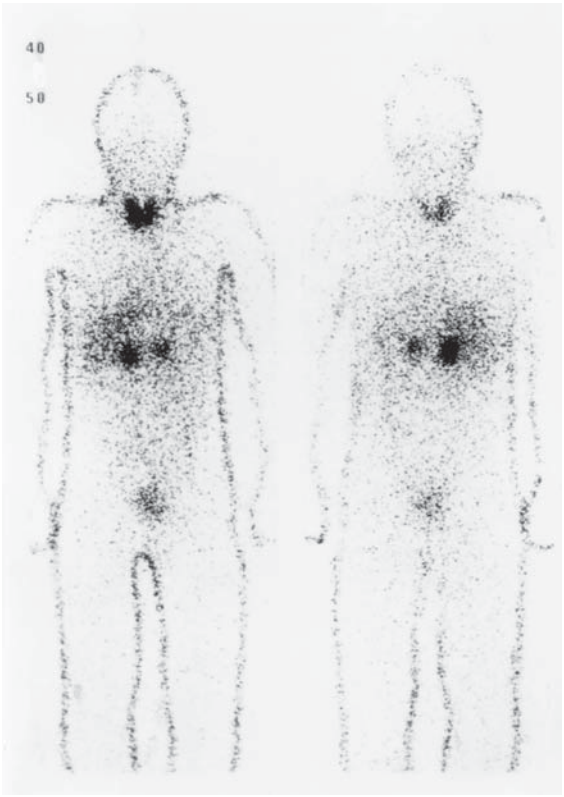


Fig. 3. (**A**) Axial CT image of the abdomen showing bilateral adrenal tumors; (**B**) ^{131}I-MIBG scintigraph showing accumulation of the bilateral adrenal tumors and the thyroid gland.

an α blocker, and the histologic diagnosis of the adrenal tumor was pheochromocytoma (Fig. 5). Finally, he underwent total thyroidectomy (Fig. 5). No distant metastasis of the MTC was evident, and serum calcitonin and CEA levels returned to normal after the operation. The patient did not agree to the family screening.

Discussion

The patient in this case had MTC, pheochromocytoma, and multiple ganglioneuromatosis. Genetic analysis identified a heterozygous germline mutation on codon 918 in the RET gene, which is typical for a case of MEN 2B. Since MEN 2B is extremely rare compared with other familial endocrine diseases, including MEN 1 and MEN 2A, it was undiagnosed for many years. In MEN 2B, the occurrence of ganglioneuromatosis is a useful indication of this rare hereditary disease. When a proband of MEN 2B is found, family screening can be easily carried out based on the biochemical and genetic tests. The mutation, a single substitution of codon 918, is most common in MEN 2B, and the mutation Met to Thr in the codon 918 activates the receptor tyrosine kinase by binding to and phosphorylating substrates other than tyrosine kinase such as c-abl and c-src *(2-4)*. This "gain of function" mutation of the RET gene leads to tumorigenesis in MEN 2B.

MTC is the first tumor to develop in patients with MEN type 2 syndrome and is the most common cause of death among those patients. Particularly in MEN 2B, MTC has been reported to be aggressive and early diagnosis and surgical treatment are extremely important. Although biochemical tests including calcitonin stimulation test are used for the early diagnosis of MTC, clinically useful direct DNA tests are now available to identify gene carriers before any clinical or biochemical abnormality occurs. Furthermore, total thyroidectomy at a very young age has been reported based on the DNA screening tests *(5,6)*. Unfortunately, an early diagnosis of the MTC was not made in the present case, and family screening was not available. Although surgical

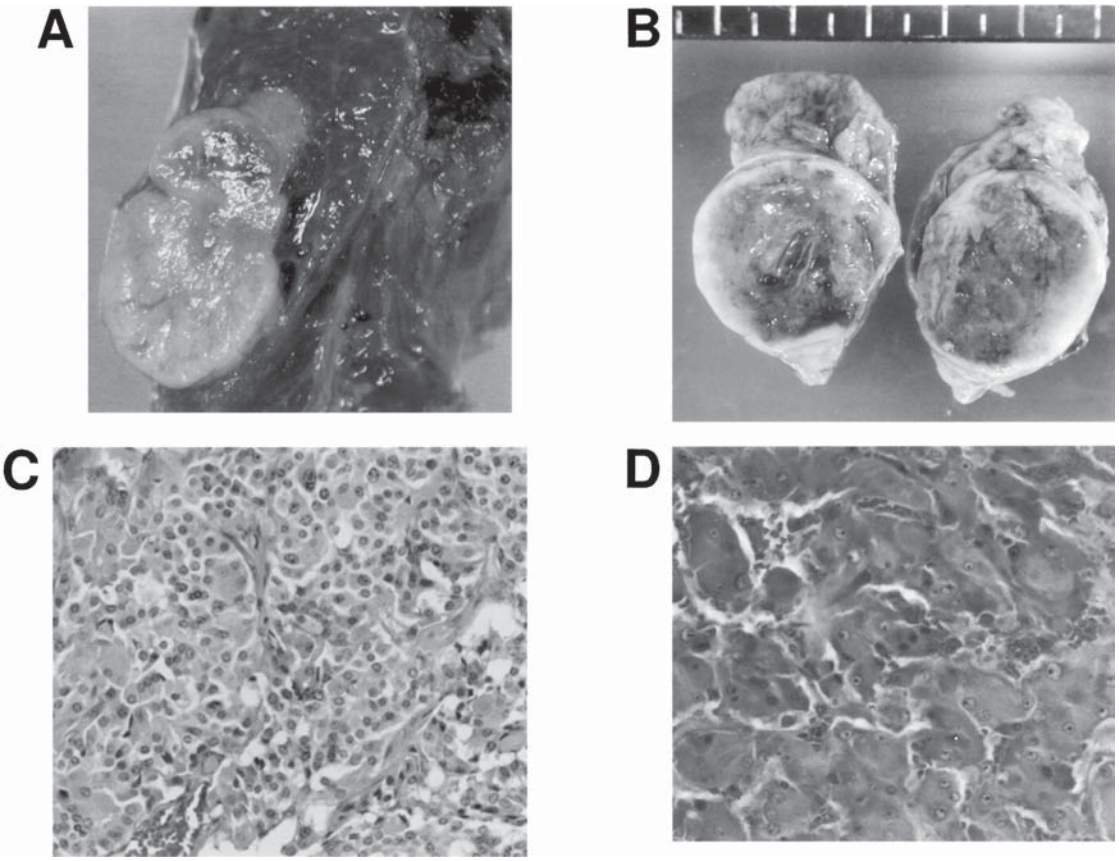


Fig. 5. (**A**) Section of the thyroid with a single tumor in the right lobe; (**B**) histology of thyroid tumor showing that the tumor was composed of solid proliferative tumor cells; (**C**) section of the right adrenal tumor and (**D**) histology of adrenal tumor showing that tumor cells such as medullary hyperplasia proliferated, typical of pheochromocytoma.

treatment of the MTC was successful in this case, careful follow-up is required.

Pheochromocytomas associated with MEN 2B are often bilateral in contrast to sporadic pheochromocytoma. Thus, bilateral adrenalectomy is often indicated in MEN 2B patients. In the present case, right adrenalectomy was performed although bilateral pheochromocytomas were revealed because the patient did not agree to removal of both pheochromocytomas because of the necessity of receiving lifelong glucocorticoid replacement therapy after the operation. We chose to remove the right pheochromocytoma, which was markedly larger than the left. After the operation, serum and urinary catecholamine levels decreased but were still higher than the normal ranges. We plan to discuss with the patient a second operation to remove the left pheochromocytoma.

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