Diagnosis of Multiple Endocrine Neoplasia Type 2A in Patients With Positive Thyroid Imaging by Iodine-131 Metaiodobenzylguanidine Scintigraphy

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Abstract: We retrospectively analyzed iodine-131 metaiodobenzylguanidine (I-131 MIBG) scintigraphy in 320 patients (male, 108 cases; female, 211 cases; average age, 45 ± 15 years). All patients received thyroid block before examination between 2007 and 2010 in our department. Various degrees of radioactivity were found in the thyroid glands or thyroid region after bilateral thyroid surgery, in addition to bilateral or unilateral abnormal radioactivity in the adrenal glands in 3 patients. These cases were confirmed for medullary thyroid carcinoma and adrenal pheochromocytoma by pathology after surgical removal of the glands, and the diagnosis of multiple endocrine neoplasia type 2A was established from the patients' history and genetic examination. The possibility of medullary thyroid carcinoma should be considered on the finding of abnormal radioactivity in the thyroid or thyroid region by I-131 MIBG scintigraphy after excluding normal radioactivity in the thyroid. When significant abnormal radioactivity is seen in the adrenal gland on I-131 MIBG scintigraphy, the possibility of adrenal pheochromocytoma should be considered. Adrenal pheochromocytoma cannot be excluded when adrenal uptake is increased. The possibility of multiple endocrine neoplasia type 2A should be considered taking into account the history of these patients.

Key Words: multiple endocrine neoplasia-2A, adrenal pheochromocytoma, medullary thyroid carcinoma, iodine-131 metaiodobenzylguanidine (I-131 MIBG)

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Iodine-131 metaiodobenzylguanidine (I-131 MIBG) scintigraphy is mainly used for localization of pheochromocytoma. It has been reported that I-131 MIBG can also be uptaken by medullary thyroid carcinomas (MTCs).[1] We retrospectively analyzed I-131 MIBG scintigraphy in 320 patients (male, 108 cases; female, 211 cases; average age, 45 ± 15 years) from 2007 to 2010 in our department. We found various degrees of radioactivity in the thyroid glands or thyroid region after bilateral thyroid surgery, in addition to abnormal bilateral or unilateral radioactivity in the adrenal glands in 3 patients. These cases were confirmed as MTC and adrenal pheochromocytoma by pathology after surgical removal of the glands, and the diagnosis of multiple endocrine neoplasia (MEN) type 2A (MEN-2A) was established from the patients' history and genetic examination.

Multiple endocrine neoplasia (MEN) is a neoplastic syndrome manifesting as hyperfunction of the endocrine glands and multiple endocrine gland tumors or hyperplasias, which can develop simultaneously or successively. It is an autosomal dominant genetic disease with high penetrance. The prevalence of MEN type 2 (MEN-2) is about 1 per 3 million people. MEN-2A constitutes approximately 75% of all cases of MEN-2. Almost all MEN-2A patients have MTC and 50% have pheochromocytoma.

CASE 1

A 39-year-old man experienced discomfort in the right side of his neck 9 years ago and was diagnosed with space-occupying lesions in the right thyroid. He underwent right total thyroidectomy, and postoperative pathologic analysis revealed a medullary thyroid carcinoma. An examination conducted 8 years ago revealed a residual mixed mass in the left thyroid. A medical examination conducted 5 years ago revealed a solid tumor mass in the left retroperitoneal space. He underwent left adrenalectomy, and postoperative pathologic analysis revealed an adrenal pheochromocytoma. During a follow-up visit 4 years ago, a solid retroperitoneal lesion (2.70 × 1.75 cm) was observed in the right retroperitoneal space and suspected to be an adrenal tumor. Last year, he underwent left total thyroidectomy for a nodule in the left thyroid that had been progressively increasing in size for 8 years; postoperative pathologic analysis revealed an MTC with cervical lymph node metastasis. Recently, the patient underwent I-131 MIBG scintigraphy, which revealed abnormal radioactivity in the right side of his neck (Fig. 1A); the right adrenal gland also showed radioactivity (Fig. 1B). He underwent right-side neck dissection, and postoperative pathologic analysis revealed a recurrence of MTC. The postoperative pathologic analysis conducted after surgery on the right adrenal gland revealed an adrenal pheochromocytoma. Relevant family history was as follows: the patient's mother died of thyroid cancer and his sister had undergone surgery for adrenal pheochromocytoma.

CASE 2

A 51-year-old woman was found to have an increased carcinoembryonic antigen level (42.7 ng/mL) during a primary examination conducted 4 years ago, and hence a more detailed examination was performed. The examination revealed sigmoid polyps, a solid mass in the right thyroid gland, multiple thyroid nodules in the left thyroid gland, and a mass in the left adrenal gland. She underwent right thyroidectomy and lymph node dissection; postoperative pathologic examination revealed an MTC. The patient was given Euthyrox (Merck KGaA, Germany) for postoperative replacement therapy. In the follow-up examinations, her calcitonin levels were found to be high. Three years ago, she underwent left adrenalectomy, and postoperative pathologic examination revealed an adrenal pheochromocytoma. She was recently hospitalized for high blood glucose levels without any obvious cause, and I-131 MIBG scintigraphy performed at 24 hours and 48 hours revealed abnormal focal radioactivity in the left thyroid gland (Fig. 2A) and increased radioactivity in the right adrenal gland (Fig. 2B). The pathologic examination conducted after left thyroidectomy revealed an MTC.

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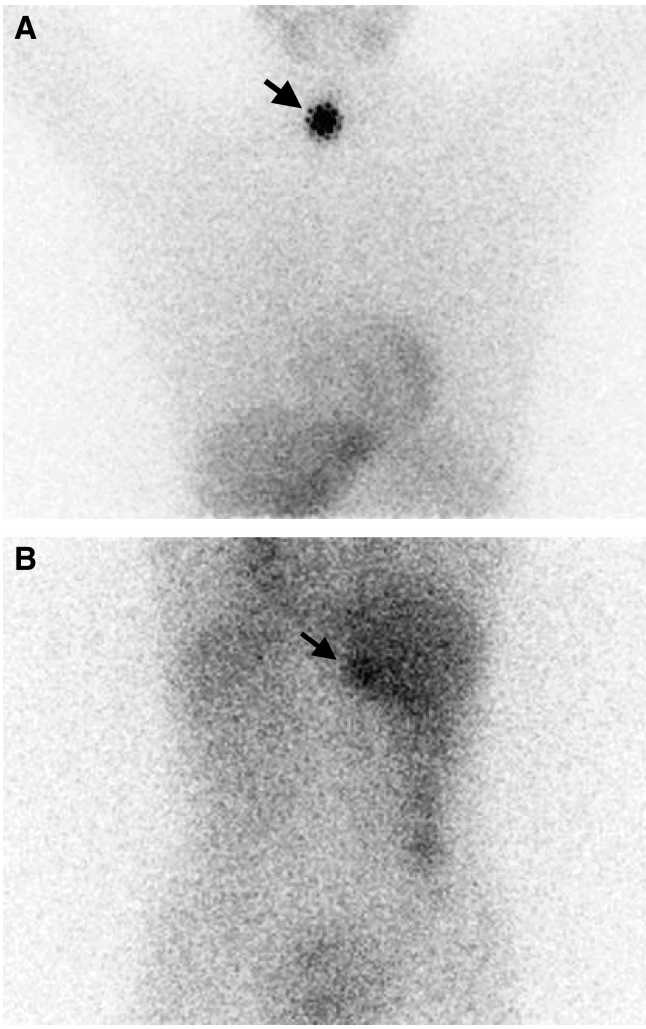

FIGURE 1. I-131 MIBG scintigraphy revealed abnormal radioactivity in the right side of the neck (**A**); the right side of the adrenal gland also showed radioactivity (**B**).

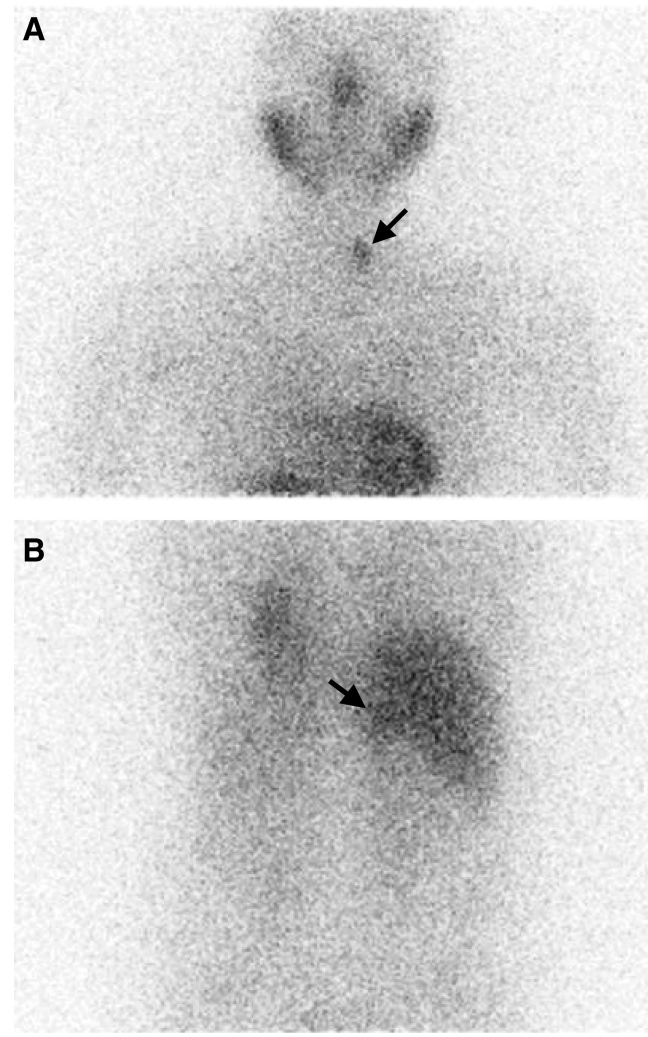

FIGURE 2. I-131 MIBG scintigraphy showed abnormal focal radioactivity in the left thyroid gland (**A**) and increased radioactivity in the right adrenal gland (**B**).

CASE 3

A 32-year-old man was found to have bilateral adrenal masses on ultrasound imaging performed during a medical examination. Computed tomography (CT) also revealed multiple bilateral adrenal masses, which were considered to be multiple adenomas, and probably pheochromocytomas. Postadmission examinations found a plasma norepinephrine concentration of 639.4 pg/mL (reference range, 19–121 pg/mL), blood epinephrine concentration of 980.3 pg/mL (reference range, 14–90 pg/mL), urinary free epinephrine concentration of 105.78 μg/24 hours (reference, $<$22 μg/24 hours), urinary free norepinephrine concentration of 284.13 μg/24 hours (reference range, 7–65 μg/24 hours), and calcitonin concentration of 505.12 pg/mL (reference range, 0.1–10.0 pg/mL). Abdominal CT angiography revealed bilateral adrenal masses, which were suspected to be pheochromocytomas. Neck ultrasonography revealed bilateral thyroid nodular lesions; one of the nodules on the right thyroid had coarse calcification. Neck CT revealed nodular low-density lesions with calcification in both thyroid glands. Regional I-131 MIBG scintigraphy revealed radioactivity in both thyroid glands; radioactivity was clearly observed on 48-hour delayed imaging (Fig. 3A). Both adrenal glands exhibited abnormal radioactivity (Fig. 3B). The patient underwent bilateral adrenal resection of the pheochromocytomas through the abdominal approach. The postoperative pathologic analysis revealed a giant adrenal pheochromocytoma. One month later, the patient underwent bilateral total thyroidectomy; the postoperative pathologic analysis revealed bilateral MTC. Relevant family history was as follows: the patient was an offspring of a consanguineous marriage; his father died of intestinal tumor, his mother has diabetes, one of his sisters died of diabetes, and another sister has adrenal pheochromocytoma.

DISCUSSION

All of the patients received Lugol solution 3 times per day, 5 drops each time, for 5 days before I-131 MIBG scintigraphy. Lugol solution was given continually for 2 days after I-131 MIBG scintigraphy for thyroid block. Abnormal radioactivity in the thyroid was observed in 3 patients; there was no abnormal radioactivity in the thyroid in the other patients in the same I-131 MIBG scintigraphy group. In case 1, after thyroidectomy, I-131 MIBG scintigraphy revealed abnormal radioactivity in the right thyroid; there was no abnormal radioactivity in the thyroid in the other 9 patients in the same I-131 MIBG scintigraphy group, which excluded the presence

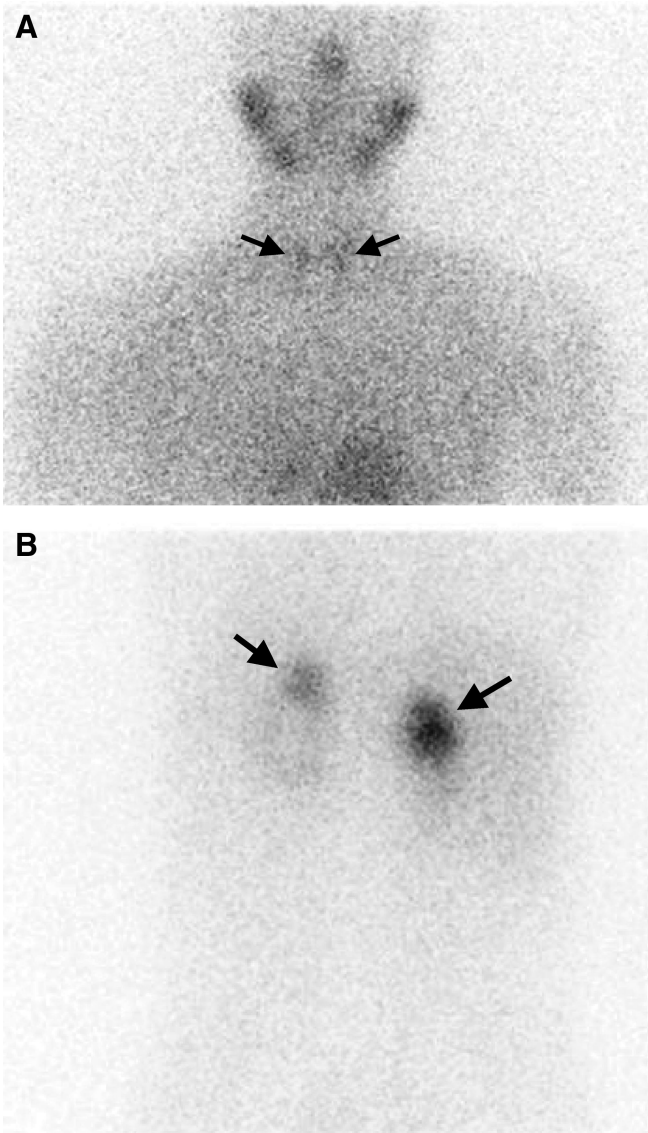

FIGURE 3. Regional I-131 MIBG scintigraphy indicated radioactivity in both thyroid glands; radioactivity was clearly observed on 48-hour delayed imaging (**A**). Both the adrenal glands exhibited abnormal radioactivity (**B**).

of free I-131 in conjugated drugs. Subsequent surgery proved that this abnormal radioactivity was caused by recurrence of MTC. In case 2, after right total thyroidectomy and lymph node dissection, I-131 MIBG scintigraphy showed local radioactivity in the left thyroid. Case 3 was in the same group as case 2 for I-131 MIBG scintigraphy; I-131 MIBG scintigraphy of the thyroids did not yield a clear image, but revealed a spotty distribution of highly radioactive regions. In the other 11 patients in that group, I-131 MIBG scintigraphy did not reveal radioactivity in the thyroid. Therefore, when I-131 MIBG scintigraphy reveals radioactivity in the thyroid, the patient should be screened carefully. In particular, the possibility of MTC should be considered in cases that are excluded from normal thyroid imaging.

A variety of techniques for imaging MTCs are available in nuclear medicine. Tc-99m dimercaptosuccinic acid is considered the gold standard for localizing medullary carcinomas. This technique has a sensitivity of up to 100%.[2,3] The sensitivity of I-131 MIBG for MTC is only 20% to 64%[1,4–6] and the specificity is only 30%.[7] Endo et al[1] found that I-131 MIBG scintigraphy can be used to diagnose MTC. Oishi et al[8] measured the catecholamine levels of 3 medullary cancer patients and found that catecholamine could be detected in all patients with medullary carcinoma; this was not possible in individuals with normal thyroid tissue. This finding also suggests the feasibility of using I-131 MIBG for diagnosing MTCs. The sensitivity of indium-111 octreotide imaging in the diagnosis of MTC is 29% to 77%.[9–11] At an early stage, the thyroid lesions of patients with MEN-2A are usually multifocal, and 95% of the patients have bilateral MTC.[12,13] The thyroid lesions in cases 1 and 2 were secondary changes, whereas in case 3, bilateral thyroid lesions were detected simultaneously with the primary changes.

Adrenal imaging was positive in these 3 patients in addition to abnormal radioactivity in the thyroids or thyroid region. The diagnosis of MEN-2A was established from patients' history and genetic examinations. In case 1, I-131 MIBG scintigraphy showed abnormal radioactivity not only in the thyroid region but also in the right adrenal gland. This was later confirmed as adrenal pheochromocytoma by pathologic examination. This patient was previously found to have right and left thyroid masses, diagnosed as MTC after surgery. Adrenal pheochromocytoma was found in both adrenal glands during routine physical examination. In case 2, radioactivity was significantly increased in the left thyroid but only slightly increased in the right adrenal gland on I-131 MIBG scintigraphy. This patient had been previously found to have medullary carcinoma in the right thyroid gland and, later, pheochromocytoma in the left adrenal gland. In case 3, a significant increase of radioactivity was found in both sides of the thyroid and also in the adrenal glands. Pathologic examination showed bilateral MTC and adrenal pheochromocytoma. Therefore, the possibility of MTC and adrenal pheochromocytoma should be considered taking into account the patient's history, and the diagnosis of MEN-2A should also be considered when a significant increase of radioactivity is found in both sides of the thyroid and the adrenal glands. In MEN-2A, pheochromocytoma and medullary carcinoma can develop simultaneously; otherwise, medullary carcinoma is usually present before pheochromocytoma appears. About 9% to 27% of MEN-2A cases manifest primarily as pheochromocytoma.[14,15]

Although all 3 patients were found to have space-occupying lesions in the adrenal or thyroid gland on medical examination, only case 3 showed a significant increase in both blood metanephrine and normetanephrine, and urinary epinephrine and norepinephrine, and none of the patients had obvious symptoms. In MEN-2A, about 30% to 50% of pheochromocytomas are asymptomatic.[16,17]

According to previous reports, the incidence rate of bilateral pheochromocytoma in MEN-2A patients is 35% to 80%.[18–20] Therefore, when I-131 MIBG scintigraphy in an MEN patient reveals abnormally high radioactivity in both adrenal glands, the possibility of bilateral adrenal pheochromocytoma should be considered. This has been confirmed in case 3, who had bilateral adrenal pheochromocytomas. If the diagnosis of unilateral adrenal pheochromocytoma is confirmed, the contralateral adrenal gland should be monitored carefully during follow-up visits. When I-131 MIBG scintigraphy reveals localized and significantly high radioactivity, the possibility of adrenal pheochromocytoma should be considered. Even if the contralateral adrenal gland shows only mild radioactivity, the possibility of an adrenal pheochromocytoma should not be excluded. Adrenal medullary hyperplasia is the early form of pheochromocytoma in MEN-2A syndrome, and eventually develops into pheochromocytoma.[21] Cases 1 and 2 were both found to have contralateral adrenal lesions in follow-up examinations after the resection of the pheochromocytoma in the left adrenal gland.

Depending on the glands affected by lesions, MEN is divided into 2 types; namely, MEN type 1 and MEN-2. On the basis of different clinical manifestations, MEN-2 tumors are further divided into the following 3 subtypes: MEN-2A, MEN-2B, and familial MTC. MEN type 1 principally manifests as tumors of the parathyroid gland, pancreatic islet cells, and pituitary gland, and seldom as tumors of the adrenal cortex, carcinoids, or lipomas. MEN-2A tumors are mainly MTCs, pheochromocytomas, and parathyroid tumors; MEN-2B principally manifests as MTCs, pheochromocytomas, a marfanoid habitus, and mucosal and intestinal ganglioneuromatosis.[22] These types of MEN may be of genetic or sporadic origin. All 3 patients reported in this study had MEN-2A. This might be due to the relatively small number of cases in our study or the lower prevalence of MEN-2B compared with that of MEN-2A.[23] Cases 1 and 3 had family histories of this disease, and hence their condition is considered to be of genetic origin. Case 2, however, had no related family history; therefore, the disease was considered to be sporadic.

CONCLUSIONS

The possibility of MTC should be considered following the finding of abnormal radioactivity in the thyroid or the thyroid region on I-131 MIBG scintigraphy, after excluding normal radioactivity in the thyroid. When significant abnormal radioactivity is found in the adrenal gland on I-131 MIBG scintigraphy, the possibility of adrenal pheochromocytoma should be considered. Adrenal pheochromocytoma cannot be excluded when adrenal uptake is increased. The possibility of MEN-2A should be considered, taking into account the history of these patients.

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