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【 CASE REPORT 】

Neurofibromatosis Type 1 with Concurrent Multiple Endocrine Disorders: Adenomatous Goiter, Primary Hyperparathyroidism, and Acromegaly

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Abstract:
We encountered a 70-year-old Japanese woman with neurofibromatosis type 1 (NF1) who had a history of pheochromocytoma and concurrently developed adenomatous goiter, primary hyperparathyroidism, and acromegaly. The patient had a somatotroph adenoma of the adenohypophysis that predisposed her to multinodular goiter. Three parathyroid tumors were detected by cervical ultrasonography and cervicothoracic computed tomography. Genetic analyses did not reveal genetic alterations (e.g. loss-of-function mutation) in the causative genes of endocrine tumors, including *MEN1*, *RET*, *VHL*, *CDKN1B*, and *CDKN2C*. The *NF1* gene could not be analyzed genetically due to the patient's refusal. The pathophysiologic mechanisms of endocrinopathy concurrence in NF1 remain to be elucidated.

Key words: neurofibromatosis type 1, adenomatous goiter, primary hyperparathyroidism, acromegaly

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Introduction

Neurofibromatosis (NF), an autosomal dominant hereditary multisystemic neurocutaneous disorder (1), occurs in 1 per 2,700 to 3,000 live births (2). Approximately half of NF cases are inherited, and the rest are caused by *de novo* mutations (3). Neurofibomatoses include neurofibromatosis type 1 (NF1), neurofibromatosis type 2, and schwannomatosis (4). NF1 is the most common of these 3 neurocutaneous disorders and is caused by heterozygous germline mutations in the *NF1* gene, which is located on chromosome 17q11.2 and encodes the 2,818-amino-acid (5), guanosine 5'-triphosphatase-activating protein neurofibromin, which functions in normal cells as a suppressor of the rat sarcoma viral oncogene homolog (RAS) signaling pathway (6). Loss-of-function mutations in neurofibromin increase RAS-GTP and enhance the activation of ras signaling pathways depending on the activation of Raf/MeK/ERK [MAPK] and Akt/mTOR (7). These pathways mutually interact and play a key role in regulating cell proliferation (8), and neurofibromin deficiency leads to an increased risk of developing benign and malignant tumors in affected individuals through the acquired inactivation of the functioning NF1 allele (9, 10).

NF1 is diagnosed clinically when two or more of the following seven features are identified: six or more café-au-lait spots, two or more neurofibromas, axillary or inguinal freckling, optic pathway glioma (OPG), two or more Lisch nodules, characteristic osseous lesions (e.g. scoliosis), and disease inheritance in a first-degree relative (2).

Rare cases of single or multiple concurrent endocrine disorders [e.g., pituitary adenoma (11), acromegaly (12), pituitary somatotroph adenoma in combination with follicular thyroid carcinoma and primary hyperparathyroidism (13), as well as pheochromocytoma and paraganglioma (14)] have been reported. However, while the genetic alterations of the *NF1* gene have been identified, the detailed physiopathologic mechanisms underlying endocrinopathy concurrence in NF1 remain to be elucidated (1, 15).

We herein report a patient with NF1 who had a history of pheochromocytoma and concurrently developed adenomatous goiter, primary hyperparathyroidism, and acromegaly.

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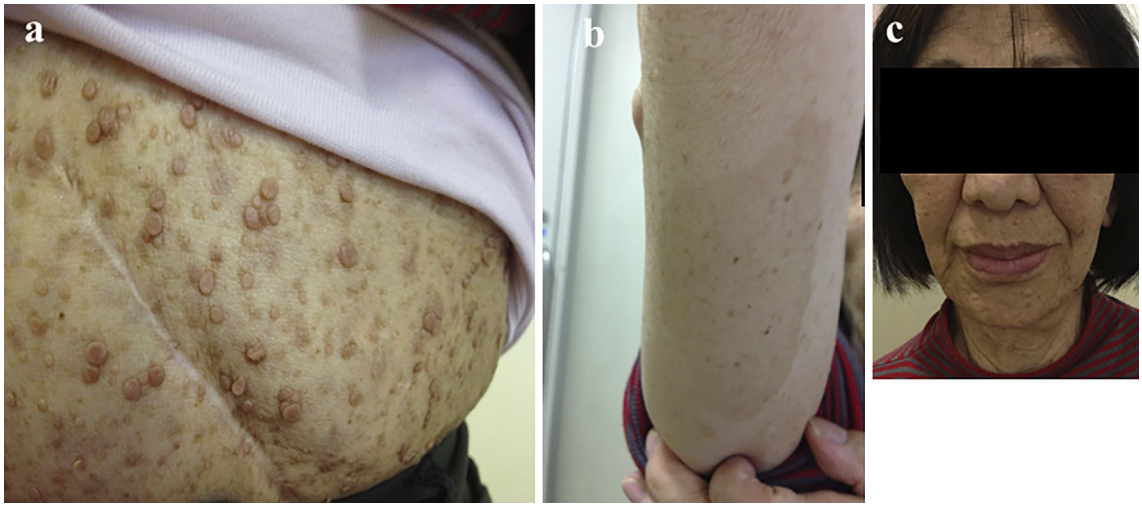

Figure 1. Skin lesions and facial features characteristic of neurofibromatosis type 1 and acromegaly. (a) Innumerable, tender neurofibromas of about 1 cm in diameter in the abdomen, with a surgical scar resulting from adrenalectomy. (b) Café-au-lait spots on the dorsal aspect of the right forearm. (c) Characteristics of neurofibromatosis (freckles around the eyelids and lips) as well as the characteristics of acromegaly (protruding mandibles and eyebrows, and a swollen nose and lips).

Case Report

A 70-year-old Japanese woman had been diagnosed with NF1 at 28 years old in the Department of Dermatology, Saitama Medical University, according to the clinical diagnostic criteria available at the time. At 48 years old, the patient had been treated for hypertension at the National Defense Medical College Hospital, where she was diagnosed with pheochromocytoma caused by a catecholamine-producing tumor of chromaffin cells in the left adrenal gland; the tumor was resected by adrenalectomy. The patient had urolithiasis in the right ureter at 63 years old and had recently noticed a palpable mass in the anterior cervical region, which prompted a referral to the Department of Endocrinology and Diabetes, Saitama Medical University. The patient had numerous painful neurofibromas about 1 cm in diameter across her whole body (Fig. 1a) as well as café-au-lait spots on the right upper arm (Fig. 1b), thighs, and abdomen. The patient presented with protruding mandibles and eyebrows, a swollen nose and lips (Fig. 1c), and enlarged limbs - clinical features of acromegaly - as well as freckles in the periorbital and perilabial regions (Fig. 1c), axillary freckling, and small Recklinghausen spots on the trunk. The patient did not have OPG but did show multiple Lisch nodules in both eyes and developed scoliosis, and her eldest son had NF1 and pheochromocytoma and had undergone adrenalectomy.

Blood tests showed no abnormalities in the blood cell count, liver function, renal function, or lipid and glucose metabolism (Table 1). The corrected serum calcium (Ca) concentration was 10.7 mg/dL (normal range: 8.5-10.5 mg/dL), and the serum phosphate concentration was 3.2 mg/dL (normal range: 2.4-4.4 mg/dL). A urinalysis did not show proteinuria or glycosuria, while the fractional excretion of Ca increased to 2.3%, which was considered responsible for the abovementioned urolithiasis.

The serum level of intact parathyroid hormone (IPTH) was 100.1 pg/mL (Table 1). In the clinical course, serum levels of IPTH were 80.0-130 pg/mL, serum Ca concentrations were 10.5-1.0 mg/dL (frequently found close to the upper limit of normal), and serum phosphate concentrations were 2.1-3.5 mg/dL (frequently found close to the lower limit of normal). The patient had never received drugs causing hypercalcemia (e.g. lithium carbonate and thiazides).

Based on these results, the patient was diagnosed with primary hyperparathyroidism. Blood samples were collected during the fast in the early morning to determine serum levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1). Serum levels of GH and IGF-1 were elevated, while serum levels of anterior pituitary hormones other than GH were normal (Table 1). Excessive GH secretion, which stimulates the hepatic secretion of IGF-1, causes acromegaly (16). The clinical picture and these laboratory results led us to suspect the presence of acromegaly.

After having confirmed that the patient did not have diabetes mellitus (DM) because plasma glucose (PG) level and serum hemoglobin A1c (HbA1c) concentration were normal at the diagnosis of concurrent endocrine disorders (Table 1), we conducted a 75-g oral glucose tolerance test (OGTT) to diagnose acromegaly (Table 2). Consequently, the serum GH levels were not found to be suppressed to <0.4 ng/mL, while the plasma blood glucose levels were increased. Before surgery, we conducted the following tests to support the diagnosis of acromegaly: 1) the luteinizing hormone-releasing stimulation test, in which serum GH levels showed a paradoxical response; and 2) the bromocriptine challenge test, in which serum GH levels decreased to less than half of the pretesting levels. Furthermore, we performed the octreo-

Table 1. Blood Tests and Urinary Excretions at the Diagnosis of Concurrent Endocrine Disorders.

Biochemical parameters (normal range)	
Fasting plasma glucose, mg/dL (70-109)	89.0
Hemoglobin A1c NGSP, % (4.6-6.2)	5.3
Albumin, g/dL (3.9-4.9)	3.8
Creatinine, mg/dL (0.34-0.79)	0.49
Serum electrolytes (normal range)	
Calcium, mg/dL (8.5-10.5)	10.5
Phosphate, mg/dL (2.5-4.5)	3.2
Serum hormones (normal range)	
IPTH, pg/mL (10.3-65.9)	100.1
GH, ng/mL (0.28-1.64)	21.6
IGF-1, ng/mL (38.0-207.0)	362.0
PRL, ng/mL (4.0-30.0)	7.6
ACTH, pg/mL (7.2-63.3)	42.1
Cortisol, μg/dL (2.3-19.4)	6.2
Adrenaline, pg/mL (<100)	24.0
Noradrenaline, pg/mL (100-450)	346
Dopamine, pg/mL (<20)	5
TSH, μIU/mL (0.39-3.98)	0.65
FT3, pg/mL (2.15-4.24)	3.26
FT4, ng/mL (1.0-1.7)	1.26
Serum tumor markers (normal range)	
Tg, ng/mL (<32.7)	5.7
Calcitonin, pg/mL (15.0-86.0)	17.0
CEA, ng/mL (<5.0)	1.7
Urine excretions (normal range)	
Metanephrine, mg/day (0.04-0.19)	0.07
Normetanephrine, mg/day (0.09-0.33)	0.19

NGSP: national glycohemoglobin standardization program, IPTH: intact parathyroid hormone, GH: growth hormone, IGF-1: insulin-like growth factor 1, PRL: prolactin, ACTH: adrenocorticotropic hormone, TSH: thyroid-stimulating hormone, FT3: free triiodothyronine, FT4: free thyroxine, Tg: thyroglobulin, CEA: carcinoembryonic antigen

Table 2. 75-g Oral Glucose Tolerance Tests, LHRH Test, Bromocriptine Test, and Octreotide Test.

	Time after the onset of 75-g OGTT at the diagnosis of acromegaly, min				
	0	30	60	120	
GH, ng/mL	13.9	21.0	41.6	30.3	
PG, mg/dL	91	179	200	141	
	Time after the onset of 75-g OGTT after the resection of a growth hormone-producing tumor in the pituitary gland, min				
	0	30	60	120	
GH, ng/mL	1.3	0.8	0.5	0.6	
PG, mg/dL	82	173	229	201	
	Time after the onset of LHRH test* at the diagnosis of acromegaly, min				
	0	30	60	120	
GH, ng/mL	14.4	290.1	101.6	27.3	
LH, mIU/mL	19.1	66.6	72.5	60.3	
FSH, mIU/mL	71.7	95.8	103.1	106.1	
	Time after the onset of bromocriptine† test at the diagnosis of acromegaly, min				
	0	120	240	360	720
GH, ng/mL	19.8	2.8	2.0	2.3	5.9
PRL, ng/mL	7.8	3.0	2.1	1.7	1.8
	Time after the onset of octreotide test‡ at the diagnosis of acromegaly, min				
	0	120	240	360	720
GH, ng/mL	19.0	1.7	0.8	0.8	2.6

*: Using 100 μg of LHRH

†: Using 2.5mg of bromocriptine

‡: Using 50 μg of octreotide

OGTT: oral glucose tolerance test, LHRH: luteinizing hormone-releasing hormone, GH: growth hormone, PG: plasma glucose, FSH: follicle-stimulating hormone, PRL: prolactin

tide challenge test, in which serum GH levels decreased rapidly after testing, thus indicating the suppression of the pituitary release of GH (Table 2).

The patient had multiple palpable nodules in the thyroid glands. However, the serum levels of free thyroxine and the tumor marker thyroglobulin were normal. Furthermore, the serum levels of tumor markers for medullary thyroid carcinoma (calcitonin and carcinoembryonic antigen) were also normal (Table 1). The patient had previously undergone adrenalectomy for a benign adrenal tumor, and her blood pressure was normal when she visited our hospital. The urinary excretions of metanephrine and normetanephrine, which are considered to be increased under conditions of pheochromocytoma, were within the normal ranges (Table 1), and the patient had neither hypertension nor intra-abdominal tumor. Therefore, we considered recurrence of pheochromocytoma not be absent.

Ultrasonography of the thyroid glands indicated a cyst (Fig. 2a) and a solid nodule (Fig. 2b) in the right lobe and solid nodules in the left lobe (Fig. 2c). Fine-needle aspiration cytology of these nodules revealed their benign nature, leading to the diagnosis of adenomatous goiter. Since blood tests and a urinalysis showed findings compatible with manifestations of primary hyperparathyroidism, we explored the site of a primary parathyroid tumor. Ultrasonography of the neck indicated a solid nodule 15 mm in diameter at the lower pole of the left lobe of the thyroid glands (Fig. 2d). Computed tomography (CT) of the cervicothoracic region showed a tumor 15 mm at the lower pole of the left lobe of the thyroid glands (Fig. 3a), a tumor 10 mm in diameter at the left side of the upper mediastinum (Fig. 3b, c), and a tumor 12 mm in diameter at the upper border of the aortic arch (Fig. 3d). These tumors were suspected of being parathyroid tumors. However, ^{99m}technetium-methoxyisobutylisonitrile (^{99m}Tc-MIBI) scintigraphy of whole body failed to identify the site of a primary parathyroid tumor (data not shown).

The bone mineral density (BMD) of the 2-4 lumbar vertebrae was 0.860 g/cm^2, which was equivalent to 85% of the

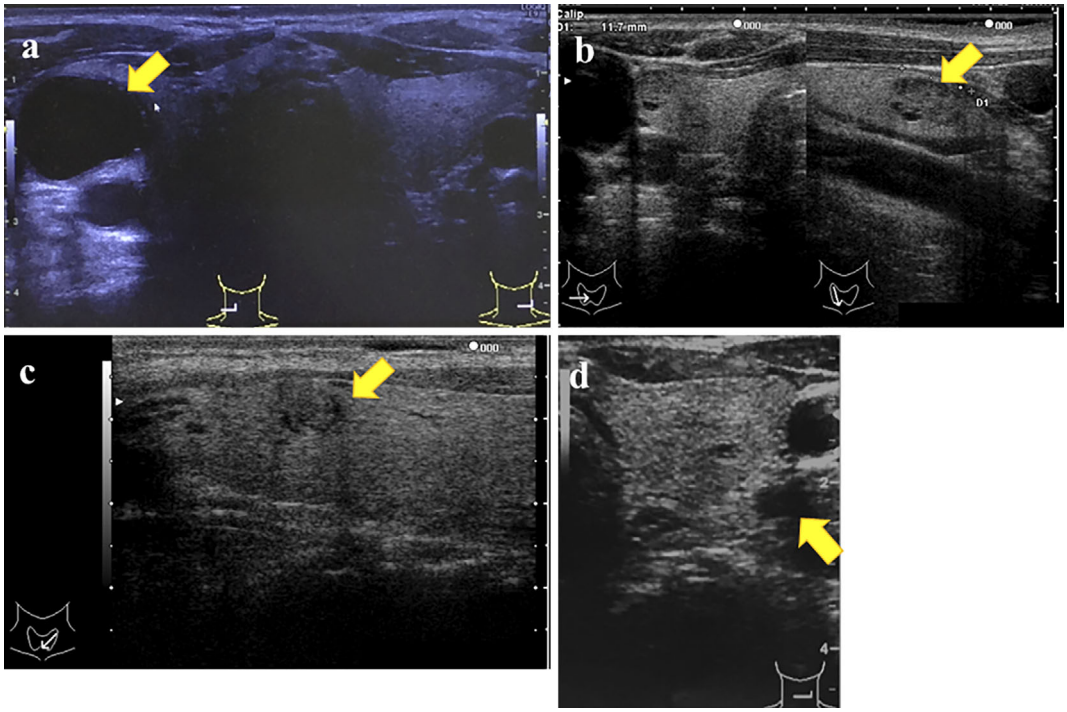

Figure 2. **Cervical ultrasonography. (a) A cyst 2 cm in diameter in the right thyroid lobe (arrow). (b) A solid nodule 9 mm in diameter in the right thyroid lobe (arrow). (c) A solid nodule 7 mm in diameter in the left thyroid lobe (arrow). (d) A solid nodule 15 mm in diameter in the lower pole of the left lobe of the thyroid glands (arrow).**

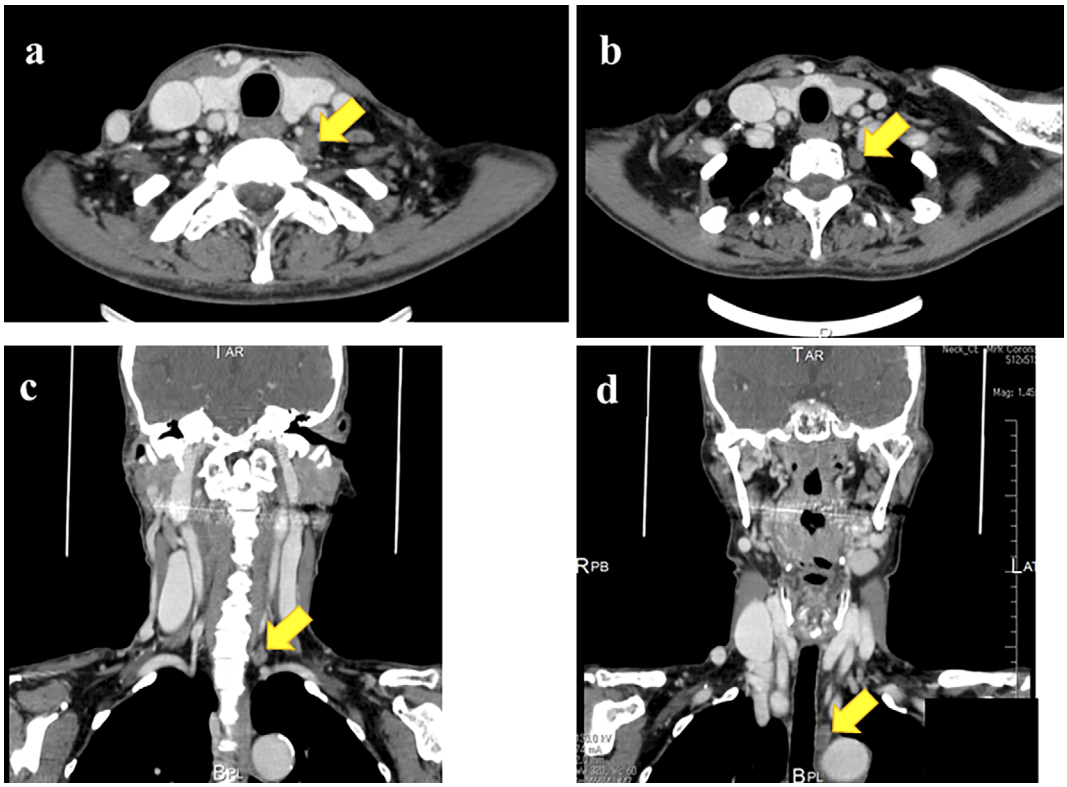

Figure 3. **Cervical computed tomography. (a) Axial tomography image showing a tumor 15 mm in diameter on the dorsal aspect of the lower pole of the left thyroid gland (arrow). (b and c) Axial and coronal images showing a tumor 10 mm in diameter on the left side of the upper mediastinum (arrows). (d) Coronal tomography image showing a tumor 12 mm in diameter at the upper border of the aortic arch (arrow).**

young adult mean. The BMD of the femoral neck was not decreased. Magnetic resonance imaging (MRI) of the pituitary gland (Fig. 4), which was conducted due to suspicion of acromegaly based on symptoms and blood test results, demonstrated a tumor in the adenohypophysis. Abdominal MRI performed in consideration of her history of pheochromocytoma showed no intraperitoneal tumors (e.g., adrenal tumors). In addition, ^{123}I-metaiodobenzylguanidine scintigraphy of whole body did not reveal any abnormal accumulation of the radioisotope (Fig. 5), indicating the development of neither recurrent pheochromocytoma nor paraganglioma. These results prompted us to consider that this patient with NF1 who had a history of pheochromocytoma had developed adenomatous goiter, primary hyperparathyroidism, and acromegaly concurrently.

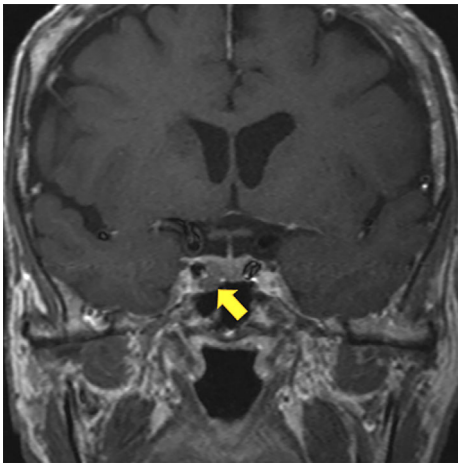

Figure 4. T1-weighted magnetic resonance imaging of the pituitary gland in the intermediate phase of gadolinium enhancement. A coronal magnetic resonance image showing a tumor 10.9×6.7 mm in size at the adenohypophysis adjacent to the right internal carotid artery (arrow).

The patient was followed up for adenomatous goiter. Regarding primary hyperparathyroidism, ^{99m}Tc-MIBI scintigraphy did not indicate the abnormal accumulation of IPTH. The BMD of the lumbar vertebrae did not decrease, the serum Ca levels were within the normal range, and the patient did not show symptoms of hypercalcemia. Acromegaly was diagnosed based on the symptoms, hematologic findings, and the presence of a primary pituitary tumor, apart from the diagnosis-supporting results of stimulation/challenge tests. The tumor was resected by endoscopic endonasal transsphenoidal surgery and histologically and immunohistochemically confirmed to be an eosinophilic adenoma with diffuse positivity for GH, indicating a typical somatotroph adenoma (Fig. 6a, b).

Cytokeratin immunostaining with CAM5.2 indicated that perinuclear patterns were more predominant than intracytoplasmic dot patterns, which led to the diagnosis of a densely granulated somatotroph adenoma (Fig. 6c). Ki-67-positive cells were scarce, with an MIB-index of 0.2% (Fig. 6d). Serum levels of GH and IGF-1 fell into the normal ranges immediately after surgery and were still low at one year later. Pituitary GH release was also normally suppressed in the 75-g OGTT that was repeated after surgery (Table 2). These results suggested that acromegaly had been treated success-

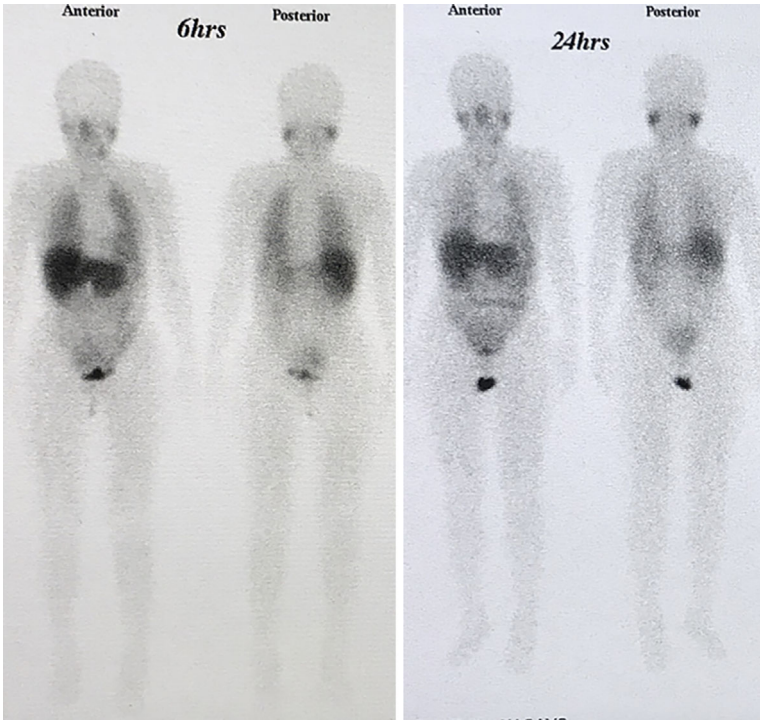

Figure 5. ^{123}I-metaiodobenzylguanidine scintigraphy. Scintigrams of the whole body showing no abnormal accumulation of the radioisotope in the cervix or abdomen, indicating the development of neither recurrent pheochromocytoma nor paraganglioma.

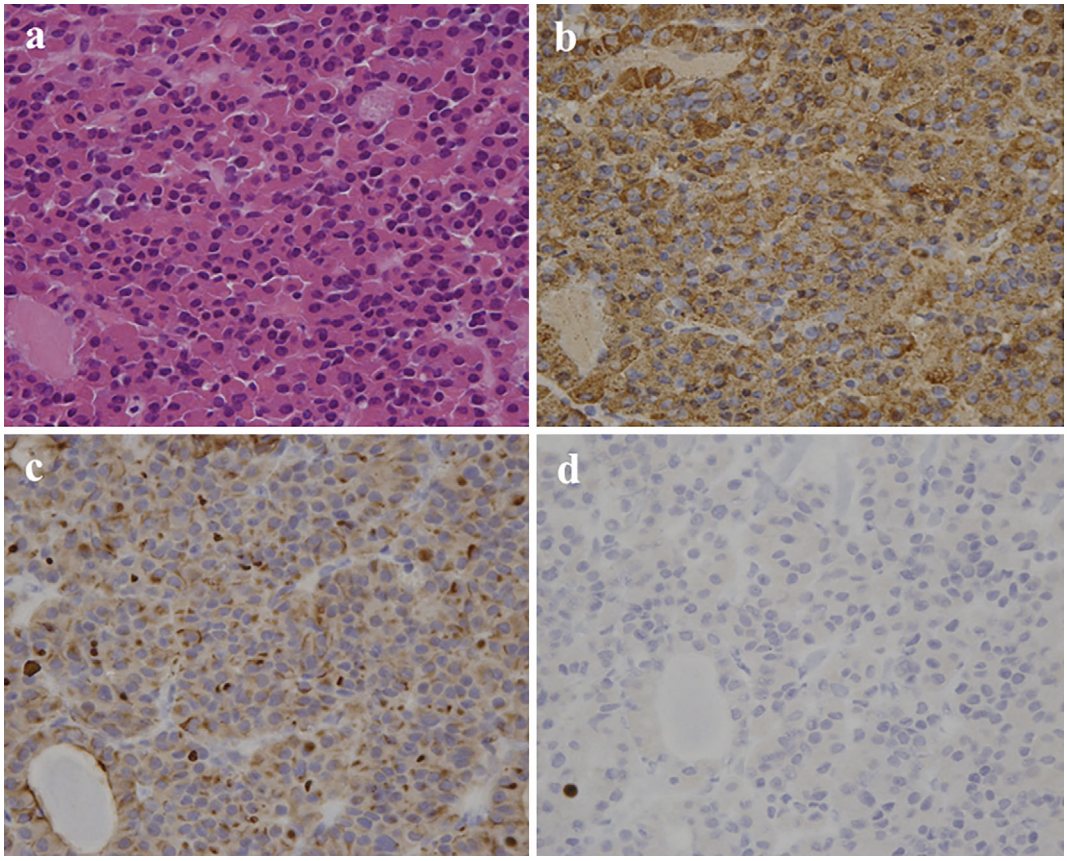

Figure 6. Histological and immunohistochemical staining of a somatotroph adenoma of the adenohypophysis. (a) Hematoxylin and Eosin staining showing an eosinophilic adenoma. (b) Immunoreactive growth hormone is diffusely stained in the cell body. (c) CAM5.2 staining showing that perinuclear patterns are more predominant than intracytoplasmic dot patterns. (d) Ki-67-positive cells are scarce, with an MIB-1 index of 0.2%.

fully by complete resection of a somatotroph adenoma of the adenohypophysis. The PG level at 120 minutes after the onset of the 75-g OGTT was 201 mg/dL, thus meeting one of the diagnostic criteria for DM. However, the serum HbA1c levels before and after surgery never exceeded 6.5% and constantly ranged between 5.2% and 5.4%. Casual blood glucose levels were 85-110 mg/dL, and DM complications (e.g., diabetic retinopathy) were not found. Hence, the definitive diagnosis of DM was not reached.

We speculated that the multiple endocrine tumors of the patient were due to mutations in the causative genes for some known endocrine tumors and thus investigated the presence or absence thereof in the multiple endocrine neoplasia type 1 (*MEN1*), MEN type 2 (*RET*), cyclin-dependent kinase inhibitor 1B (*CDKN1B*), *CDKN2C*, and von Hippel-Lindau disease (*VHL*) genes. The patient gave her written informed consent prior to conducting the analyses of these genes and received genetic counseling several times. The ethics committee and institutional review board at our hospital approved the protocol for the genetic analyses (approval numbers: 720 and 13020, respectively). All studies, including the genetic analyses, were conducted in accordance with the Declaration of Helsinki. Peripheral blood samples were collected to extract genomic DNA from peripheral leukocytes.

Unfortunately, however, the *NF1* gene could not be analyzed genetically due to the patient's refusal because she considered there to be no additional therapeutic benefits from genetic validation. The patient was thus diagnosed with NF1 based on the clinicopathologic manifestations and according to the clinical practice guidelines for NF1 published by the Japanese Dermatological Association (5). The genetic analyses of the *MEN1* and *RET* genes were conducted by FALCO Biosystems (Kyoto, Japan). All exons and the exon-intron boundaries were analyzed for the *MEN1* genes, as were exons 5, 8, 10, 11, 13, 14, 15, and 16 for the *RET* genes.

The gene variants of exons 1, 2, and 3 of the *VHL* gene in 3p25-26 were examined; however, multiplex ligation-dependent probe amplification was not performed. The forward and reverse sequence analyses of exons 1 and 2 (including the exon-intron boundaries) of the *CDKN1B* and *CDKN2C* genes, respectively, were conducted as per the published procedures (17-19). Consequently, none of these genes showed genetic alterations.

Discussion

To our knowledge, this is the first case report on an NF1 patient with a history of pheochromocytoma who concurrently developed multiple endocrine disorders (adenomatous goiter, primary hyperparathyroidism, and acromegaly). A pituitary adenoma caused GH hypersecretion and the secondary elevation of IGF-1, leading to acromegaly and adenomatous goiter (20). Our patient also had an adenomatous goiter, which is considered to be associated with acromegaly. The incidence of pheochromocytoma is higher in cases of NF1 than in other endocrine disorders (21), with an approximately 10-fold greater incidence than in healthy individuals. Walther et al. reported that the incidence of pheochromocytoma in patients with NF1 was 0.1-5.7% (21). The incidence of pheochromocytoma is greater in autopsy cases of NF1 patients; 3.3% to 13% of them presented complications (22), while 8.6% of them developed asymptomatic pheochromocytoma. The incidence of malignant pheochromocytoma ranged from 16.7% to 26.9% (23). Takayama et al. found that 60% of patients with NF1-associated, malignant pheochromocytoma had distant metastases at the time of the diagnosis and a poor prognosis (24).

A very low incidence of endocrine disorders other than pheochromocytoma has been reported in association with NF1. A review of previous case reports on NF1 patients described limited numbers of patients who developed the following concurrent endocrine disorders: primary hyperparathyroidism (25, 26), acromegaly and hypersomatotropism in children (12, 13, 27, 28), and somatostatin-producing carcinoid tumors (29). The pathogenetic mechanism by which such endocrine disorders develop in association with NF1 is unknown. There are even fewer reports on multiple endocrine disorder complications. Ercolino et al. reported a patient with multiple endocrine neoplasia type 2A (MEN2A) and identified NF1 patients with the abnormal expression of the *RET* gene (30). Gkaliagkousi et al. reported a patient with NF1 involving MEN2A and medullary thyroid carcinoma, pheochromocytoma, and primary hyperparathyroidism who had not developed missense mutations in the *RET* gene (31). In contrast, our patient had three parathyroid tumors. The development of multiple parathyroid tumors is a clinical feature of parathyroid tumors that are found in MEN 1 (32). The *MEN1* gene alterations were presumably involved in the pathogenesis of these tumors. Therefore, considering the potential genetic alterations of the related genes, we conducted genetic analyses of the *MEN1*, *RET*, *VHL*, *CDKN1B*, and *CDKN2C* genes. As a result, none of these genes showed genetic alterations; the full-length *MEN1* gene and *RET* gene showed no mutations. In addition, multiplex ligation-dependent probe amplification did not reveal a large deletion in the *MEN1* gene.

The concept of MEN4 disease originated from the discovery of patients with mutations in the genes encoding cyclin-dependent kinase inhibitor (CDKI) proteins who did not show mutations in the *MEN1* gene despite clinically presenting with MEN1's features (19). At present, MEN resulting from a mutation in the *CDKN1B* gene is called MEN4. MEN4 has been reported in a limited number of patients with hyperparathyroidism and GH- or prolactin-producing pituitary tumors (17, 18). Our patient with a history of pheochromocytoma also developed primary hyperparathyroidism and acromegaly. However, the *CDKN1B* gene did not show mutations, contrary to our speculation. We did not find any mutations in the *CDKN2C* gene, which is altered in a small number of patients presenting with no mutations in the *MEN1* gene who are clinically diagnosed with MEN. A review of previous reports on multiple endocrine disorders in NF1 patients (13) did not identify any genetic alterations. NF1 patients do not have genetic alterations that cause multiple endocrine disorders (e.g., MEN). The *NF1* gene, which is the causative gene of NF1, encodes neurofibromin, which suppresses the activity of the RAS protein, an important protein for intracellular signal transduction. Loss-of-function mutations in the *NF1* gene cause the suppression of cell proliferation and apoptosis, leading to tumorigenesis (4) as described above. These mechanisms of tumorigenesis differ from those of other diseases (e.g., MEN and VHL).

In some pediatric patients with NF1, acromegaly developed concurrently due to the loss of somatostatinergic inhibition caused by the OPG-induced activation of the mitogen-activated protein kinase (MAPK) signaling pathway when somatotroph adenoma of the adenohypophysis was absent (13, 28, 33). In contrast, not OPGs but somatotroph adenomas of the adenohypophysis developed in some adult patients with NF1 who had acromegaly concurrently (12, 13). In sporadic pituitary adenomas, changes in the cell signaling pathways - PI3K/Akt/mTOR and Raf/MEK/ERK - are implicated in the pathogenesis of NF1 (34). In this regard, the increased expressions of B-Raf and Akt, as well as the increased activity of B-Raf- and Akt-activated components were found in pituitary adenomas (35). Based on these findings, Checa Garrido et al. recognized a good chance of developing pituitary adenomas due to genetic alterations of the *NF1* gene (12).

Of special note was the fact that our patient with a history of pheochromocytoma developed not only a somatotroph adenoma of the adenohypophysis but also primary hyperparathyroidism. In addition, our patient had multiple parathyroid tumors as culprit lesions of primary hyperparathyroidism - a clinical presentation resembling MEN1. The tumorigenic mechanisms underlying the genetic alterations in the *MEN1* gene, as well as the *CDKN1B* and *2C* genes, which are the causative genes of MEN4, are descried briefly. The mutated *MEN1* gene blocks the normal binding of menin to the *CDKN1B* or *2C* gene in the regulatory domain, thereby suppressing the transcription of these genes. This suppressed transcription causes a failure in cell proliferation control and promotes tumorigenesis (36). In contrast, the pathogenic mechanism of MEN4 is based on mutations in the *CDKN1B* or *2C* genes themselves, leading to the fail-

ure of cell proliferation control and promotion of tumorigenesis (36, 37). We speculate that a pathologic condition resembling MEN1 or MEN4 occurred in our patient through the following putative mechanisms: 1) mutations in unidentified factor (s) other than menin that positively regulate the transcription of the *CDKN1B* and *CDKN2C* genes in the regulatory domain, resulting in the impairment of the normal transcription of the affected genes; and 2) aberrations (e.g. silencing and epigenetic modification) in the posttranscriptional mechanisms of these genes.

Conclusions

We encountered an NF1 patient with a history of pheochromocytoma who concurrently developed multiple endocrine disorders, namely adenomatous goiter, primary hyperparathyroidism, and acromegaly. In contrast, we did not find any genetic alterations in the causative genes of endocrine tumors (*MEN1*, *RET*, *VHL*, *CDKN1B*, and *CDKN2C*). The further accumulation of clinicopathologic and genetic data of NF1 patients with multiple endocrine disorders may help clarify the pathophysiologic mechanisms involved in endocrinopathy concurrence in NF1.

The authors state that they have no Conflict of Interest (COI).

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