A Case of Neurofibromatosis Type 1 Coinciding with Bilateral Pheochromocytomas, Multiple Gastrointestinal Stromal Tumors, and Malignant Peripheral Nerve Sheath Tumor

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Abstract

Neurofibromatosis type 1 (NF1) is associated with benign and malignant neoplasms, but the coincidence of abdominal neoplasms is rare. A 65-year-old woman with NF1 had episodes of nausea, tachycardia, hypertension, and loss of consciousness. Bilateral adrenal tumors were detected by abdominal computed tomography, and plasma and urinary catecholamine levels were elevated. Open bilateral adrenalectomy and histological findings revealed bilateral pheochromocytomas (PCCs). Furthermore, malignant peripheral nerve sheath tumor (MPNST) and multiple gastrointestinal stromal tumors (GISTs) were incidentally found in the abdominal cavity. Early diagnosis of abdominal neoplasms in NF1 patients is important because of the risk of malignancy, organic complications and hemorrhagic-obstructive complications.

Key words: neurofibromatosis type 1, pheochromocytoma, gastrointestinal stromal tumor, malignant peripheral nerve sheath tumor

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Introduction

Neurofibromatosis type 1 (NF1) is an autosomal dominant disorder with an incidence of approximately 1 in every 3,000 individuals without racial differences (1). The pathogenesis of NF1 is based on mutations of the *NF1* tumor suppressor gene, which generally cause a decreased production of the intracellular neurofibromin protein. This leads to increased Ras signaling to downstream effectors, including Ras/mitogen-activated protein kinase (MAPK) and the Akt/mammalian target of rapamycin (mTOR) (2). Clinical expression in NF1 is extremely variable, including neoplastic or non-neoplastic disorders, primarily involving tissues of neuroectodermal or mesenchymal origin in different regions, such as the skin, bone, eye, and central nervous system. Furthermore, neoplastic lesions, such as neurofibromas, malignant peripheral nerve sheath tumors (MPNSTs), pheochromocytomas (PCCs), and gastrointestinal stromal tumors

(GISTs), can also arise in the abdominal region of NF1 patients (3). However, there are few reports regarding the occurrence of neoplasms in the abdominal region. We report a rare case of NF1 occurring with bilateral PCCs, multiple GISTs, and MPNST in the abdominal cavity.

Case Report

A 65-year-old woman had chest pain and palpitation, and was admitted to a hospital for possible unstable angina. However, cardiac computed tomography angiography showed no evidence of coronary artery stenosis. When she was in that hospital, she had frequent episodes of nausea, tachycardia, hypertension, and loss of consciousness. Abdominal computed tomography (CT) showed bilateral adrenal tumors. PCC was considered as a potential cause of her symptoms, and she was transferred to our hospital for further examination. She was diagnosed with NF1 at 16 years of age based on the clinical findings and frequently under-

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Table 1. Endocrinological Examination on Admission

	Values	Normal range
ACTH (pg/mL)	22.2	7.2-63
Cortisol (μg/dL)	11.7	4.0-19.3
PRA (ng/mL/hr)	3.7	0.2-2.7
PAC (ng/dL)	7.5	3-16
DHEA-S (mg/dL)	33	13-154
Adrenaline (ng/mL)	0.43	<0.17
Noradrenaline (ng/mL)	1.4	0.15-0.57
Dopamine (ng/mL)	<0.02	<0.03
<Urine>		
Adrenaline (μg/day)	197.0	3.4-26.9
Noradrenaline (μg/day)	445.0	48.6-168.4
Dopamine (μg/day)	390	365-961
Metanephrine (mg/day)	3.3	0.04-0.19
Normetanephrine (mg/day)	3.2	0.09-0.38
HVA (mg/g · cre)	7.1	1.6-5.5
VMA (mg/g · cre)	30.9	1.2-4.9

PRA, plasma renin activity; PAC, plasma aldosterone concentration; DHEA-S, dehydroepiandrosterone sulfate; HVA, homovanillic acid; VMA, vanillylmandelic acid

went surgical excision of general neurofibromas in the skin, right femur, and thoracic cavity. At 56 years, she experienced an ileus due to an intestinal tumor. She underwent tumor resection, and histological examination revealed GIST. At 58 years, a right adrenal tumor was detected using abdominal CT; however, she did not attend follow-up visits. There was no family history of NF1. Physical examination indicated that her height was 152 cm, weight was 53 kg, and body mass index (BMI) was 22.9. Her blood pressure was 99/49 mmHg and pulse rate was 79 beats/min. Physical examination revealed typical neurofibromas over all of her skin and café-au-lait spots on her trunk and extremities.

The results of endocrinological examination upon admission are shown in Table 1. Plasma adrenaline and noradrenaline, as well as urinary adrenaline, noradrenaline, metanephrine, normetanephrine, homovanillic acid (HVA), and vanillylmandelic acid (VMA) levels following 24-h urine collection were markedly increased. Plasma levels of aldosterone and cortisol were within normal limits. An abdominal CT scan showed a round tumor with cystic degeneration approximately 7 cm in diameter located in the right adrenal gland, a solid tumor with partial cystic degeneration approximately 2 cm in diameter located in the left adrenal gland, and a hypervascular tumor approximately 3 cm in diameter located in the duodenal second portion (Fig. 1). ¹²³I-metaiodobenzylguanidine (MIBG) scintigraphy showed abnormal accumulations over the bilateral adrenal masses (Fig. 2). However, ¹⁸F-fluorodeoxyglucose positron emission tomography (FDG-PET) showed no accumulation on adrenal tumors, and no other abnormal uptake was observed. We diagnosed PCCs in bilateral adrenal glands and GIST in the duodenum associated with NF1. After preoperative treatment using an alpha-blocker (doxazosine mesilate), open bilateral adrenalectomy was performed. During surgery, multiple small nodules were observed on the serosal surface of the

gastric posterior wall. Because intraoperative frozen section diagnosis of this nodule confirmed GISTs, resection of the duodenum nodule was not performed. The postoperative course was uneventful and the patient made an excellent recovery. The patient was treated with a tyrosine kinase inhibitor (imatinib mesilate) for multiple GISTs, and there was no evidence of disease progression 1 year after operation.

Histology and immunohistochemistry

The right adrenal tumor was 8×8×6 cm in size, and hemorrhagic fluid leaked out from a cut section (Fig. 3A). Microscopic examination revealed the oval to polygonal cells with abundant cytoplasmic granules and fascicular patterns were consistent with PCC (Fig. 3B). Immunohistochemical studies indicated positivity for S-100, synaptophysin, and chromogranin A, thereby confirming PCC. The Ki-67 (MIB-1) labeling index was less than 1%. The left adrenal tumor appeared as a solid mass 1 cm in size, and pathologic and immunohistochemical findings were identical to those of the right adrenal tumor (Fig. 3C, D). Furthermore, a tumor with cystic and hemorrhagic changes was located outside the left adrenal gland (Fig. 3C). This tumor was 2.2×1.2 cm in size, and pathologic findings showed dense proliferation of spindle-shaped cells with nuclear atypia (Fig. 3E). The Ki-67 index was approximately 1.5%. The tumor was positive for S-100, CD56, and CD34 and was diagnosed as low-grade MPNST. Nodules located around the posterior wall of the stomach were 4 to 6 mm in size (Fig. 3F). Histologically, these nodules consisted of the proliferated spindle cells with fibrosis (Fig. 3G). Immunohistochemically, tumor cells were positive for KIT and CD34, indicating GIST (Fig. 3H). The Ki-67 index was less than 1%.

Discussion

NF1, described in detail by von Recklinghausen in 1882, is characterized by the presence of café-au-lait spots, cutaneous neurofibromas, and neoplasms of the peripheral or central nervous system (4). Some neoplasms can occur in the abdominal region of NF1 patients; abdominal neoplasms are divided into 5 categories: neurogenic tumors, neuroendocrine tumors, non-neurogenic gastrointestinal stromal tumors, embryonal tumors, and miscellanea (3). However, the coincidence of these neoplasms in the abdominal region is very rare. Previous case reports in English literature describing the concurrence of PCC and GIST in NF1 are summarized in Table 2. Because positive staining for KIT has been required for the diagnosis and nosology of GISTs since 1998, it is possible that these tumors were reported as separate tumors in previous reports (5). To our knowledge, there have been 8 documented cases, including the present case, of concurrent PCC and GIST (6-11), and only 2 cases of concurrent PCC, GIST, and MPNST (11). PCCs are generally bilateral, and GISTs are generally multiple. However, it is not clear whether these concurrences are incidental or these neoplasms are related to NF1 because of the low

Figure 1. A and B: Abdominal computed tomography (CT) scan showed a right adrenal mass with cystic degeneration, a left adrenal mass with a partial cystic degeneration, and a hypervascular tumor located in the duodenal second portion (indicated by arrows).

Figure 2. ^{123}I -MIBG scintigraphy showed increased uptake over the bilateral adrenal masses (indicated by arrows).

prevalence of NF1.

PCCs arise from the chromaffin cells of the adrenal medulla. Although PCCs are more frequently observed in NF1 patients than in the general population, they were found to occur in only 0.1% to 5.7% of NF1 patients (12). Bausch et al. showed that of 37 NF1 subjects with PCC, 62% had solitary adrenal tumors, 27% had bilateral adrenal disease, and 6% were identified as malignant PCC (13). GISTs are mesenchymal neoplasms arising from the interstitial cells of Cajal (ICC) of the myenteric plexus, the pacemaker cells regulating autonomic motor activity (14). These cells show immunohistochemical positivity for KIT or platelet-derived growth factor receptor- α (PDGFRA), which is transmembrane receptor regulating cell proliferation. Although GISTs are also more frequently observed in NF1, they were found to occur in only 3.9% to 25% of NF1 pa-

tients (14, 15). GISTs in NF1 patients are generally multiple and are predominantly located within the small intestine (14, 15). Surgical tumor excision is the primary treatment method for localized GIST in NF1. In cases of diffuse or metastatic disease, the KIT-related tyrosine kinase inhibitors (such as imatinib mesilate) have been considered the standard treatment, showing an up to 80% response rate (3). MPNSTs are the most common malignant neoplasm in NF1. Approximately 30% to 50% of NF1 patients have benign plexiform neurofibromas, and 8% to 13% of these patients undergo malignant transformation to MPNSTs (16). MPNSTs primarily arise in the retroperitoneum and remain silent until they increase in volume, involving surrounding structures, thereby producing pain, obstruction, and neurological deficits. Moreover, there are no observable radiological features on CT or MRI that can be used to clearly differ-

Figure 3. A: Macroscopic findings showed a right adrenal tumor 8×8×6 cm in size with hemorrhagic degeneration. B: Histological staining (Hematoxylin and Eosin: H&E) of the right adrenal tumor was consistent with pheochromocytoma. C: Left adrenal tumor was 1 cm in size and the tumor outside the left adrenal gland was 2.2×1.2 cm in size with cystic and hemorrhagic change. D: Histological staining (H&E) of the left adrenal tumor was consistent with pheochromocytoma. E: Histological staining (H&E) of the tumor outside the left adrenal gland was consistent with low-grade MPNST. F, G: Nodules located on the gastric serosal surface were 0.4 to 0.6 cm in size. Histologically, these nodules consisted of proliferated spindle cells with fibrosis. H: Immunohistochemically, tumor cells of the stomach were positive for KIT, indicating GIST.

entiate benign plexiform neurofibromas from those that have transformed into MPNST. Primary treatment includes radical excision of the tumor, even if the role of surgery is limited to palliative debulking (3). Although these gastrointestinal and retroperitoneal manifestations are rarely seen in NF1 patients, they are associated with NF1. Early diagnosis of these manifestations is very important because of the risk of malignancy, organic complications such as those associated with PCC, and hemorrhagic-obstructive complications such as those associated with tumors of the gastrointestinal tract (3). However, in patients with abdominal neoplasms,

the diagnosis may be delayed if the patient has no related symptom, since there are no standard guidelines for abdominal imaging. Furthermore, there may be problems such as the shortage of highly specialized clinicians and institutions, inadequate knowledge of clinicians, patient's ignorance, and social inhibitions that prevent patients from visiting a hospital. In future, it is important to establish treatment systems that enable multidisciplinary management of abdominal manifestations.

The *NF1* gene is a tumor suppressor gene mapped to chromosome 17q11.2 and encoding the cytoplasmic protein

Table 2. Review of Previous Case Reports with the Coincidence of PCC and GIST in NF1

Patient age, sex	PCC Location/Diameter	GIST Location/Diameter	MPNST Location/Diameter	Others	References
82, f	lt adrenal gland/5 cm (composite PCC-ganglioneuroma)	gastric serosa(multiple)/0.3-0.5 cm		clitoral neurofibroma	Lisewski et al. 2006 (6)
64, m	rt adrenal gland/0.7 cm, lt adrenal gland/6 cm	small intestine and its mesentery(multiple)/0.2-4 cm			Bümming et al. 2006 (7)
53, f	lt adrenal gland/5 cm	small intestine/3 cm		astrocytoma	Nemoto et al. 2006 (8)
63, f	rt adrenal gland/3 cm, lt adrenal gland/5 cm	ileum/6.5 cm, jejunum/3 cm			Kramer et al. 2007 (9)
60, f	lt adrenal gland/3 cm	small intestine(multiple)/0.5-2 cm			Teramoto et al. 2007 (10)
67, f	bilateral/n.i.	mesentery of the descending colon/3 cm			Teramoto et al. 2007 (10)
48, m	rt adrenal gland/8 cm, lt adrenal gland/2 cm (composite PCC-MPNST)	gastric serosa(multiple)/up to 0.5 cm, jejunum serosa/8 cm and 2 cm	spleen, diaphragm, bilateral pleurae, lungs, lymph nodes/up to 3 cm		Sakaguchi et al. 1996 (11)
65, f	rt adrenal gland/8 cm, lt adrenal gland/1 cm	duodenum/3 cm, gastric serosa(multiple)/0.4-0.6 cm	outside the left adrenal gland/2 cm		Present case

PCC, Pheochromocytoma; GIST, gastrointestinal stromal tumor; MPNST, malignant peripheral nerve sheath tumor; n.i., no information

neurofibromin (2). In Japan, genetic screening for the *NF1* gene, including prenatal screening, is not conducted because of the large size of the *NF1* gene and absence of a mutational hotspot, and there is very little correlation between genetic variation and severity of illness (1). Furthermore, an accurate diagnosis of NF1 is generally possible based on its characteristic phenotype and family history without genetic screening. Biallelic inactivation of *NF1*, with one allele constitutionally inactivated and the other somatically mutated, is required for benign and malignant tumor formation (17). Accordingly, evidence of *NF1* loss of heterozygosity (LOH) has been observed in PCC (13), GIST (18, 19), and MPNST (20-22). However, the molecular mechanisms of NF1 tumorigenesis remain unclear. Growth factors interact with receptors at the cell surface, activating guanine nucleotide exchange factors and activating Ras. Activated Ras sends intracellular signals, activating the MAPK pathway, resulting in cell proliferation. Activated Ras also activates the phosphoinositide 3 kinase (PI3K), Akt, and mTOR pathways, protecting cells from apoptosis. Neurofibromin down-regulates Ras through its GAP-related domain; thus, at decreased levels in NF1, signaling is increased through all of these pathways, resulting in cell proliferation and inhibition of apoptosis (2). NF1-associated GISTs were reported to lack *c-kit* or *PDGFRA* mutations, which are typically observed in sporadic GIST (14, 15, 23). Because the mutations

of *c-kit* result in constitutive activation of the Ras/MAPK pathway as well as of the Akt/mTOR pathway, overlapping signaling pathways may be involved in the molecular pathogenesis of NF1-associated GIST and sporadic GIST (24). Activation of the Ras pathway may develop hyperplasia in ICC, ultimately leading to GIST. Similarly, NF1-associated PCCs reportedly lack succinate dehydrogenase subunit D (*SDHD*) mutations, which are typically observed in nonfamilial PCC (13). These findings also suggest that activation of the Ras/MAPK pathway increases proliferation of chromaffin cells in the adrenal medulla, leading to PCCs. MPNSTs typically grow out of a preexisting plexiform neurofibroma (16). Subsequent genetic alterations on benign neurofibromas result in progression toward MPNST development. A number of genetic changes, including losses of *TP53*, *RBI*, and *CDKN2A*, as well as several oncogenes and cell-cycle genes, have been implicated in MPNST development (22). Furthermore, increasing LOH of the *NF1* gene region is correlated with varying degrees of malignant transformation (22). Further studies, including molecular analysis to clarify the mechanisms of tumorigenesis in NF1, are necessary.

We observed a case of coincident bilateral PCCs, multiple GISTs, and MPNST in the abdominal cavity. To our knowledge, this is the second case report of these 3 disorders occurring simultaneously in the same patient with NF1. In pa-

tients with NF1, early diagnosis of these abdominal manifestations is very important because of the risk of malignancy, organic complications and hemorrhagic-obstructive complications. However, the diagnosis of these abdominal manifestations may be delayed in many cases. In the future, it will be important to establish treatment systems that enable multidisciplinary management of abdominal manifestations.

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

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