

Coexistence of Gastrointestinal Stromal Tumors (GISTs) and Pheochromocytoma in Three Cases of Neurofibromatosis Type 1 (NF1) with a Review of the Literature

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Abstract

It is well known that neurofibromatosis type 1 (NF1) is uncommonly associated with pheochromocytoma development and also, to a larger extent, with gastrointestinal stromal tumors (GISTs). We herein document three cases with the rare condition of NF1 coexisting with GIST and pheochromocytoma, while one of them also has a composite tumor and another has papillary thyroid carcinoma.

Key words: neurofibromatosis type 1 (NF1), pheochromocytoma, composite tumor, gastrointestinal stromal tumor (GIST), papillary thyroid carcinoma

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Introduction

Neurofibromatosis type 1 (NF1) is one of the most common dominantly inherited disorders, with a prevalence of 1 in 3,000 live births in Western countries (1, 2). This condition is also known as von Recklinghausen's disease. Seven diagnostic criteria for NF1 have been defined by The National Institutes of Health Consensus Statement (3), with two or more of the following criteria required to make a diagnosis: six or more café au lait macules (>5 mm in size in pre-pubertal patients and >15 mm in size in post-pubertal patients); either two or more neurofibromas or one or more plexiform neurofibromas; axillary or inguinal freckling; two or more Lisch nodules; optic gliomas; specific osseous dysplastic lesions; or a first-degree relative with NF1 diagnosed according to the above criteria. The cause of NF1 is a mutation in the *NF-1* tumor suppressor gene mapped to chromosome 17q11.2. The *NF-1* gene encodes a 2,818-amino acid protein called neurofibromin, which inhibits the *Ras* oncogene activity; the loss of neurofibromin results in *Ras* activation and tumor formation (4).

Despite the well-known genetic basis of the disease, genetic screening is not necessary in most patients.

Neoplastic lesions, such as neurofibromas, malignant peripheral nerve sheath tumors, pheochromocytoma tumors, carcinoid tumors and gastrointestinal stromal tumors (GISTs), can also arise in the abdominal region among NF1 patients (5). Pheochromocytoma lesions originate from the chromaffin cells of the adrenal medulla, occurring in approximately 1% of patients with NF1, whereas composite tumors of the adrenal medulla are much rarer. By definition, a composite tumor consists of a pheochromocytoma lesion associated with neuroblastoma, ganglioneuroblastoma or ganglioneuroma. GISTs are rare tumors that arise from Cajal cells in the myenteric plexus. GISTs are the most common mesenchymal neoplasms of the gastrointestinal tract and have been described in association with NF1. Papillary thyroid carcinoma is the most common thyroid malignancy, arising from follicular cells in the thyroid gland. We herein report the coexistence of GIST and pheochromocytoma in three patients with NF1 and review the relevant literature.

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Figure 1. Dispersed cutaneous neurofibromas and multiple café au lait spots on the skin of the patient

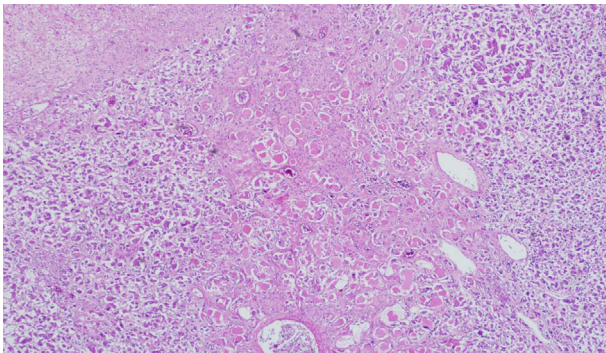


Figure 3. The tumor in the adrenal tissue containing pheochromocytoma and ganglioneuroma areas

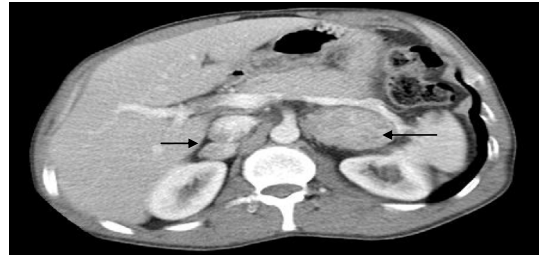


Figure 2. Appearance of bilateral adrenal masses with heterogeneous-density by abdominal computerized tomography

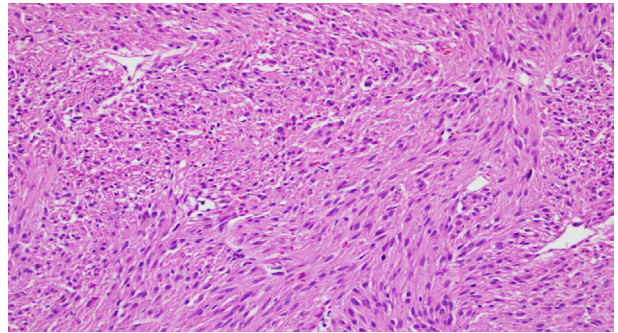


Figure 4. Tumoral mass that composed of spindle and epithelioid cells without atypia

Case Report

Case 1

A 47-year-old normotensive [blood pressure (BP): 110/70 mmHg] man was admitted due to bilateral adrenal masses identified during the course of spontaneous pneumothorax. Multiple cutaneous neurofibromas and more than 20 café au lait spots with widths ranging from 1 to 6 cm were detected (Fig. 1) on a physical examination. Based on these findings, von Recklinghausen's disease was diagnosed. The patient stated that his father, grandfather and brothers all had similar skin lesions.

An abdominal CT scan revealed bilateral adrenal masses with heterogeneous density. The diameter of each mass was approximately 7 cm on the left adrenal gland and 2 cm on the right adrenal gland (Fig. 2). During the clinical investigation, very high levels of 24-hour urinary catecholamine metabolites [metanephrine and normetanephrine: 2,856 and 5,949 (upper limits: 341 and 444) μg , respectively] were detected. Other adrenocortical parameters (aldosterone and cortisol) were normal. Based on these findings, pheochromocytoma was subsequently diagnosed, and cortical-sparing

adrenalectomy for bilateral pheochromocytoma was performed. During surgical exploration, Meckel's diverticulum was also noticed incidentally in the ileum and also excised. On the histopathological examination, a pheochromocytoma in the right adrenal gland and composite tumor (pheochromocytoma plus ganglioneuroma) in the left adrenal gland were found (Fig. 3). On the other hand, a GIST was detected in the specimens obtained from the resection of Meckel's diverticulum (Fig. 4). On immunohistochemical staining of the GIST, both CD117 and CD34 were found to be positive in more than 50% of the tumor cells (Fig. 5a, b).

A corticotropin stimulation test with 1 mg of synacthen was performed three days after surgery, indicating a normal cortisol response. In addition, normal levels of 24-hour urinary catecholamine metabolites (metanephrine and normetanephrine: 64 and 326 μg , respectively) were detected two weeks after the surgical procedure.

Case 2

A 50-year-old hypertensive (BP: 150/85 mmHg) man with von Recklinghausen's disease was admitted to due to bilateral adrenal masses noted on radiological imaging performed to assess right-sided pain. The diameter of each adrenal mass was 4.5 cm on the right and 3.5 cm on the left (Fig. 6). On the physical examination, multiple cutaneous neurofibromas and more than six café au lait spots with widths above 15 mm were detected on the patient's body, including the limbs (Fig. 7a, b). Furthermore, the patient reported that his mother, brother and daughter had similar café

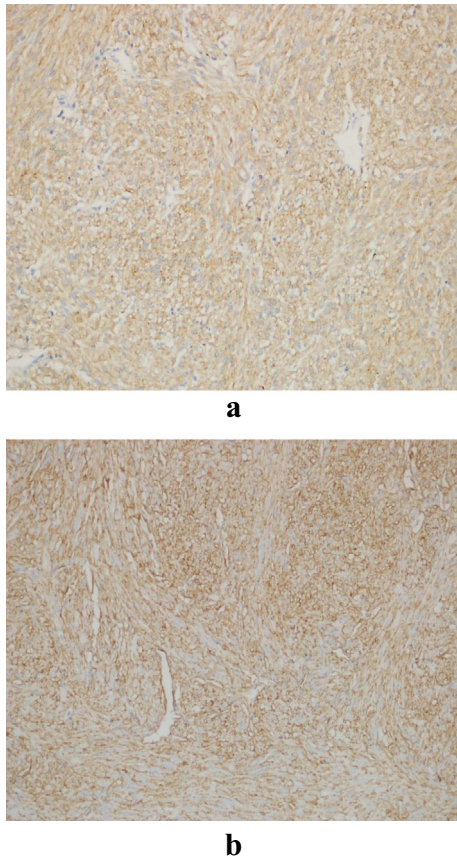


Figure 5. Diffuse positivity in tumor cells with CD117 and CD34

au lait spots. In addition, he had been using an antihypertensive drug (candesartan: 16 mg/day). A Lisch nodule was detected on an ophthalmological examination.

According to the clinical investigation, the 24-hour urinary metanephrine level was 2,633.25 μg , which is approximately 8-fold higher than the upper limit of normal; however, the 24-hour urinary normetanephrine level was not elevated, and the patient's adrenocortical function was normal. Pheochromocytoma was subsequently diagnosed, and, following preoperative preparation, total adrenalectomy of the right adrenal mass and cortical-sparing adrenalectomy of the left adrenal mass were performed. During surgical exploration, many nodular lesions were detected in the jejunum, one of which was removed.

According to the findings of a histopathological examination, a diagnosis of bilateral pheochromocytoma was determined. Additionally, GIST was detected in the specimens obtained from the jejunum. More than 50% of the GIST cells exhibited a positive immunoreaction of CD117, whereas CD34 was negative.

Normal levels of 24-hour urinary metanephrine and normetanephrine (23.24 and 366.6 μg , respectively) were detected seven weeks after surgical intervention. Unfortunately, at the same time, a corticotropin stimulation test with 1 mg of synacthen was performed; however, an inadequate cortisol response was achieved, and glucocorticoid treatment was initiated for adrenal insufficiency.

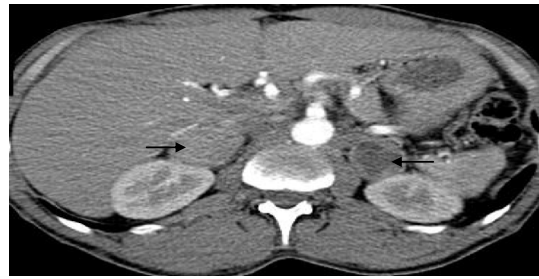


Figure 6. Bilateral adrenal masses in the patient with NF1

Case 3

A 43-year-old normotensive (BP: 120/80 mmHg) man was referred to our clinic due to a right adrenal mass (approximately 5.5 cm) discovered incidentally. According to a physical examination, multiple cutaneous neurofibromas and more than six cafe au lait spots with a width above 15 mm were identified on the patient's body. In addition, there was a plexiform neurofibroma in the right axillary region (Fig. 8a, b). The patient reported that his daughter had similar skin lesions, with the exception of plexiform neurofibroma. Based on these findings, von Recklinghausen's disease was diagnosed. An ophthalmological examination revealed bilateral multiple Lisch nodules.

During to the clinical investigation, very high levels of 24-hour urinary catecholamine metabolites (metanephrine and normetanephrine: 7,629.12 and 3,380.4 μg , respectively) were measured. Other adrenocortical parameters were in the normal ranges. An ultrasonographic examination of the thyroid gland showed multiple thyroid nodules. An ultrasound-guided fine needle aspiration (FNA) biopsy was performed of the suspected nodules. As a result, a malignant cytology (Bethesda 2009) was detected in the specimens obtained from the isthmus nodule, the cytopathological findings of which were compatible with a diagnosis of papillary carcinoma. The first operation was planned to treat the mass on the right adrenal gland due to the presence of pheochromocytoma. During surgical exploration, in addition to the pheochromocytoma, a second mass was unexpectedly found in the small intestine; both masses were removed.

According to a histopathological examination of the masses, a pheochromocytoma was detected in the right adrenal gland and a GIST (Fig. 9) was detected in the specimens obtained from the small intestine. Immunohistochemistry showed a positive reaction for CD117 (+++) in more than 50% of the GIST cells. At the same time, strongly positive CD34 staining was observed in all GIST cells (Fig. 10a, b).

After surgery, the basal cortisol level was found to be normal, and a corticotropin stimulation test was not required because the patient underwent unilateral adrenalectomy. Seven days later, normal levels of 24-hour urinary catecholamine metabolites (metanephrine and normetanephrine: 93.8 and 482 μg , respectively) were observed.

Two months after the first operation (for pheochromocytoma), bilateral thyroidectomy plus cervical lymph node dis-

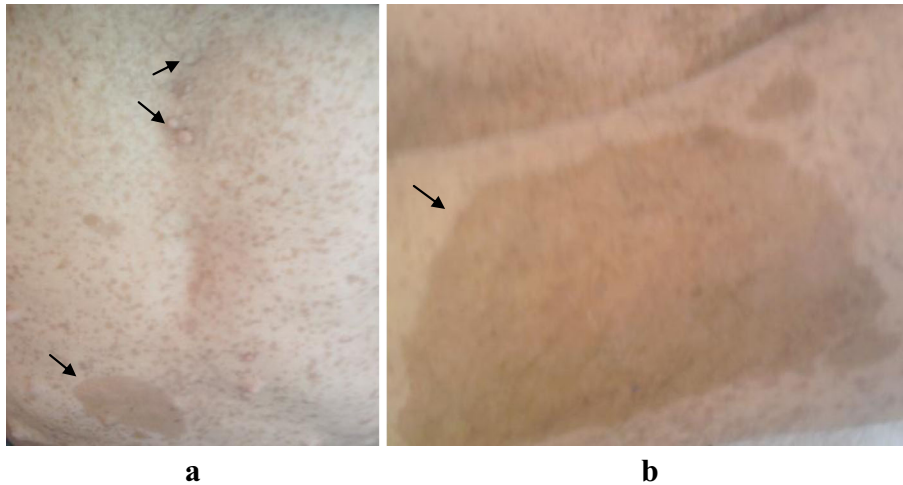


Figure 7. Multiple neurofibromas and café au lait spots on the skin of the patient, and close-up of the broad café au lait spots on the lower extremity of same patient

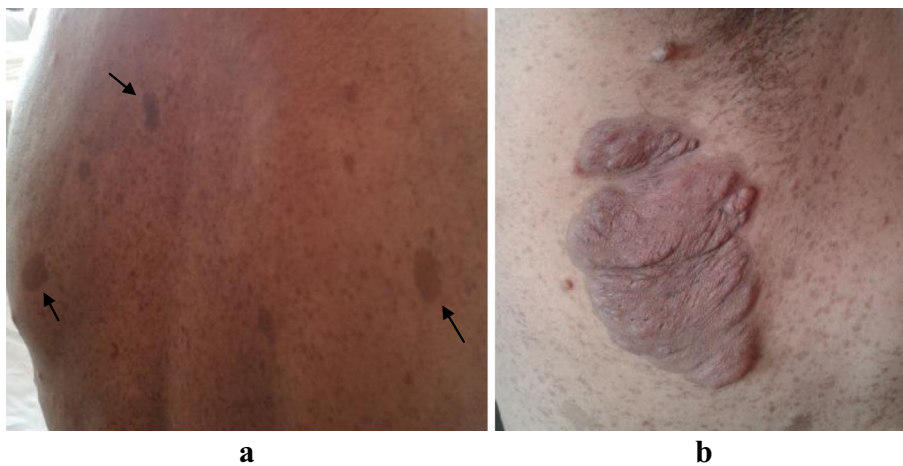


Figure 8. Multiple café au lait spots on the patient's back, and plexiform neurofibroma on the right axillary region of same patient

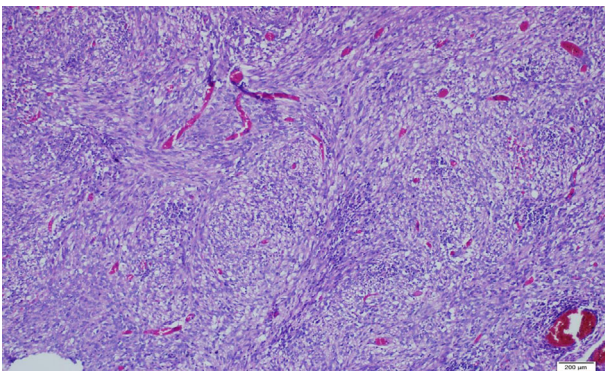


Figure 9. The mesenchymal tumor composed of spindle and epithelioid cells that significantly without atypia

section was performed, and the diagnosis of papillary thyroid carcinoma was confirmed. According to a histopathological examination, multifocal papillary carcinoma was detected in three distinct foci (the isthmus, right thyroid lobe

and left thyroid lobe: 12 mm, 4 mm and 1 mm, respectively), and cervical lymph nodes metastases of papillary carcinoma were identified. The patient is currently being followed for both pheochromocytoma and papillary thyroid carcinoma.

Discussion

Although adrenal tumors are unilateral in most of cases of pheochromocytoma, they are often bilateral in patients with a hereditary background. Four main syndromes are known to be associated with inherited pheochromocytoma: von Hippel-Lindau Syndrome (vHL), Multiple Endocrine Neoplasia Syndrome type 2A and 2B (MEN 2A and 2B), NF1 and Familial Paraganglioma Syndrome. Among these syndromes vHL, MEN 2A and 2B pheochromocytomas are usually bilateral, whereas bilaterality in NF1 is rare. Some tumors have a histological variant, called composite pheochromocytoma (including ganglioneuroma elements). There-

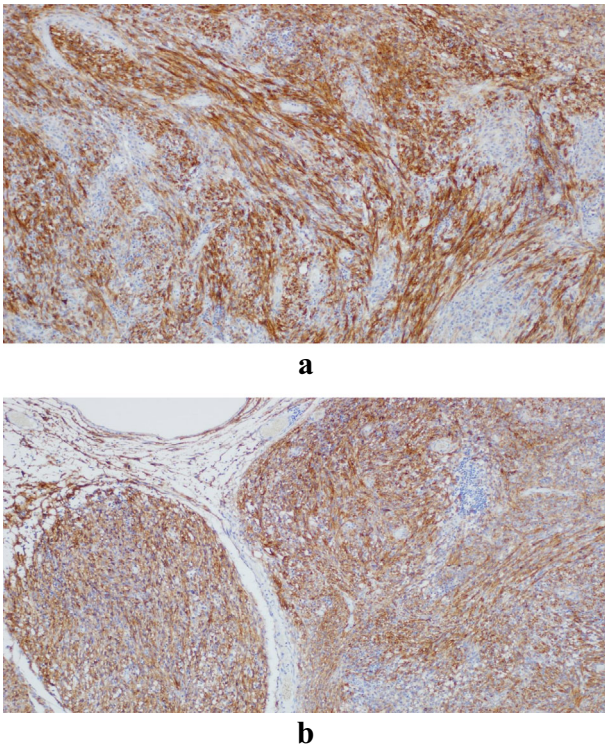


Figure 10. Tumor cells diffusely strongly positive CD117 and CD34

fore, the first two cases had bilateral pheochromocytoma, with a composite tumor of pheochromocytoma observed in the former.

Mutations in the *NF1* gene, which plays a role as a tumor suppressor gene, result in the loss of functional proteins associated with a wide spectrum of clinical findings, including the development of NF1-associated tumors. The protein encoded by NF1, neurofibromin, downregulates the *Ras* activity. *Ras* activates a number of signaling pathways, such as the stem cell factor (SCF)/c-KIT signaling and mitogen-activated protein kinase (MAPK) pathways.

Patients with NF1 have an increased risk of developing gastrointestinal tumors, including rare types, such as GISTs (6). In addition, GISTs are increasingly being recognized in cases of NF1. The incidence of GISTs among NF1 patients varies from 3.9% to 25%, while the overall ratio of NF1 among GIST patients reaches up to 6% (7). Although most GISTs harbor activating somatic mutations of KIT and platelet-derived growth factor alpha receptor (PDGFRA), the absence of such mutations in NF1-associated GISTs (NF1-GISTs) is likely indicative of a different pathogenetic mechanism (8). Somatic NF1 mutations have been identified in the interstitial cells of Cajal (ICC) throughout the gastrointestinal tract, as well as NF1-GISTs lacking KIT or PDGFRA mutations (9). The inactivation of neurofibromin in the absence of KIT or PDGFRA mutations is an alternate mechanism leading to GIST formation. Furthermore, increased signaling via the Ras/MAPK pathway has also been demonstrated in NF1-GISTs compared to that observed in non-NF1 associated GISTs. The activation of the *Ras* path-

way responsible for neurofibroma formation in patients with NF1 also causes Cajal cell proliferation, ultimately leading to GIST development.

The GISTs observed in NF1 patients are generally multiple in number and predominantly located within the small intestine. Most of these tumors cause no symptoms until they grow large in size, as in our cases; however, making an early diagnosis of these lesions is important due to the risk of malignancy, systemic complications associated with pheochromocytoma and hemorrhagic-obstructive complications associated with GISTs. However, it is very rare that these three disorders (NF1, GIST and pheochromocytoma) occur simultaneously. To the best of our knowledge, there have only been 12 documented cases (10-20) of NF1 with concurrent pheochromocytoma and GIST lesions previously published in the English literature; we herein report three new cases. The characteristics of all 15 patients are summarized in Table.

Furthermore, our case is the first case of bilateral pheochromocytoma lesions with a composite tumor (pheochromocytoma plus ganglioneuroma) and a GIST in Meckel's diverticulum. We performed a search for the coexistence of GISTs and composite tumors using PubMed (www.pubmed.com) and found only two reports (19, 20). However, the GIST in our case was located in the Meckel's diverticulum, different from that observed in the other reported cases.

Meckel's diverticulum is a congenital abnormality that results from the incomplete closure of the omphalomesenteric or vitelline duct. Although Meckel's diverticulum is the most common congenital anomaly of the gastrointestinal tract, the development of tumors within a Meckel's diverticulum is rare. Likewise, Meckel's diverticulum is also an unusual site for GIST formation. Our patient had a Meckel's diverticulum complicated by a GIST. This rare combination has been previously reported in the literature (21-23); however, we could not find any reported cases of NF1 associated with a GIST in Meckel's diverticulum and a pheochromocytoma. Therefore, our case may be the first reported case to involve all three conditions concurrently.

Our second patient also had NF1, GIST and bilateral pheochromocytoma lesions, similar to our first patient; however, unlike the latter, he did not have a composite tumor. Cortical-sparing adrenalectomy was performed in both cases, although the adrenocortical function was spared after surgery in the former only. Glucocorticoid replacement therapy was started in the second case due to the development of adrenocortical insufficiency after bilateral adrenalectomy.

Our last patient had NF1, GIST, pheochromocytoma and papillary thyroid carcinoma lesions simultaneously. NF1 has been reported to be associated with a number of malignancies. However, the occurrence of papillary thyroid carcinoma associated with NF1 is very rare, with only four cases having been published in the English literature (24-27). Furthermore, the coexistence of NF1, GIST, pheochromocytoma and papillary thyroid carcinoma has not been previously reported. Therefore, this case is likely the first case to involve

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

| Patient age, sex | Pheochromocytoma Location/Diameter | GIST Location/Diameter | Others | References |
|------------------|-------------------------------------------------------------------------|--------------------------------------------------------------------------|-----------------------------|----------------|
| 48, m | right adrenal gland/8 cm, left adrenal gland/2 cm (composite PCC-MPNST) | Gastric serosa (multiple)/up to 0.5 cm, jejunum serosa/8 cm and 2 cm | MPNST | 13 |
| 82, f | left adrenal gland/5 cm (composite PCC-GN) | Gastric serosa (multiple)/0.3-0.5 cm | | 20 |
| 64, m | right adrenal gland/0.7 cm, left adrenal gland/6 cm | small intestine and its mesentery (multiple)/0.2-4 cm | | 14 |
| 53, f | left adrenal gland/5 cm | small intestine/3 cm | astrocytoma | 15 |
| 63, f | right adrenal gland/3 cm, left adrenal gland/5 cm | ileum/6.5 cm, jejunum/3 cm | | 16 |
| 60, f | left adrenal gland/3 cm | small intestine (multiple)/0.5-2 cm | | 12 |
| 67, f | bilateral/n.i. | mesentery of the descending colon/3 cm | | 12 |
| 65, f | right adrenal gland/8 cm, left adrenal gland/1 cm | duodenum/3 cm, gastric serosa (multiple)/0.4-0.6 cm | MPNST | 11 |
| 61, f | left adrenal gland/0.81-1.12 cm | duodenum (multiple) /5.44-6.29 cm | | 17 |
| 48, m | right adrenal gland/4 cm | duodenum(multiple) /1.5-3.5 cm | | 18 |
| 59, f | left adrenal gland/7 cm right adrenal gland/3,5 cm | Gastric serosa (multiple)/up to 0.2 cm, small intestine /0.8 cm and 3 cm | | 19 |
| 55, m | bilateral (composite PCC-GN) / 5.4-5.8 cm | jejunum/0.4 cm | | 19 |
| 47, m | right adrenal gland/3 cm left adrenal gland/5.5 cm (composite PCC-GN) | Meckel's diverticulum (multiple)/0.5-0.6 cm | | Present case 1 |
| 50, m | right adrenal gland/5 cm, left adrenal gland/3 cm | small intestine serosa/0.7 cm | | Present case 2 |
| 43, m | right adrenal gland/6 cm | small intestine/6 cm | papillary thyroid carcinoma | Present case 3 |

PCC: pheochromocytoma, GIST: gastrointestinal stromal tumor, MPNST: malignant peripheral nerve sheath tumor, GN: ganglioneuroma, n.i.: no information

the coexistence of all four conditions.

Papillary carcinomas constitute approximately 85% of primary thyroid malignancies; these lesions are three times more frequent in women than in men. Thyroid carcinomas occur rarely as a component of several familial syndromes involving the heritable loss of tumor suppressor genes. It is natural to consider the possibility that papillary carcinoma of the thyroid gland observed in this case was associated with the other three diseases accidentally. However, it is also possible to interpret the relationships between these diseases in such a way that NF1 appears to have mediated the other neoplasms, including the GIST, pheochromocytoma and papillary thyroid carcinoma. Likewise, we previously reported the first coexistence of NF1, breast cancer and pheochromocytoma (28).

All three patients in the present study were men in the

fifth decade of life, and none developed recurrence of pheochromocytoma during the course of postoperative follow-up, with an average duration of 14 months. Genetic consultation was recommended to all patients because their first-degree relatives were also presumably likely to have NF1.

In conclusion, patients with NF1 have a tendency to exhibit the coexistence of NF1, GIST and composite tumors (pheochromocytoma plus ganglioneuroma). In addition to other locations, Meckel's diverticulum may be a site of GIST formation in such patients. Furthermore, patients with NF1 can also develop papillary thyroid carcinomas, and our final patient is likely the first NF1 patient to present with the combination of all four conditions.

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

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