

# Neurofibromatosis type 1 associated with pheochromocytoma and gastrointestinal stromal tumors: A case report and literature review

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**Abstract.** Neurofibromatosis type 1 (NF1) is a genetic disorder associated with neurofibromin 1 (*NFI*) gene mutation, which generates an increased risk of variety of tumor types. The current study reports a case involving NF1, pheochromocytoma (PHEO) and gastrointestinal stromal tumors (GIST). A 56-year-old man presented with abdominal pain and polypnea. Clinical investigation revealed multiple diffuse soft-tissue lesions throughout his body, and pigmented macules on the skin. Imaging analyses revealed thoracic scoliosis, multiple subcutaneous nodules in the abdomen and trunk, and a 7.0x7.7x8.9-cm oval-shaped, cystic mass in the left upper abdominal cavity. Immunohistochemical staining indicated that S-100 protein and synaptophysin were highly expressed in adrenal gland neoplasm, whilst CD117 and CD34 were highly expressed in small intestine tumors. The overall clinical and pathological finding suggested a diagnosis of NF1, giant PHEO and small intestinal stromal tumor. In addition, a literature review was conducted to identify the specific clinical features of patients with this condition. Only 11 similar cases have been reported worldwide. In the present study, paroxysmal hypertension occurred in the majority of patients, and GISTs tended to be located in the small intestine. In addition, the present study demonstrated that many of the patients had a poor prognosis. Therefore, the present study indicates that NF1-PHEO-GIST

is a special type tumor with varied clinical symptoms, which may be associated with an increased risk for poor prognosis; however, more studies are required to confirm this.

## Introduction

Neurofibromatosis type 1 (NF1), which is also known as von Recklinghausen's disease, is a genetic disorder that involves autosomal-dominant mutations. The disease is characterized by skin lesions called *café-au-lait* spots and cutaneous neurofibromas (1). The prevalence of NF1 in general population is ~1 in 3,500 (2). NF1 is associated with mutations in the neurofibromin 1 (*NFI*) gene, which generate an increased risk of variety of tumor types, including benign and malignant tumors (3). Studies have suggested that 0.1-5.7% of cases of NF1 are complicated with pheochromocytoma (PHEO) (4). The incidence of PHEO is 2-8 per 1,000,000 adults (4). PHEO releases catecholamines, which results in a series of clinical manifestations that include hypertension and metabolic disorders. A total of 4-25% of patients with NF1 may also present with gastrointestinal stromal tumors (GIST) (5,6), which are the most common mesenchymal tumors of the gastrointestinal tract. GISTs are considered to occur in 20-40 per million inhabitants per year (7,8), and 20-50% of GISTs are localized in the small intestine, usually in the jejunum (7,8).

The current study presents a case of NF1 occurring with PHEO and GIST. To the best of our knowledge, this case is extremely rare. In addition, a brief literature review is presented.

## Case report

On October 23, 2013, a 56-year-old male was admitted to the Emergency Department of Ningxia People's Hospital (Yinchuan, China) for abdominal pain and fever lasting 15 days, concomitant with cough and polypnea. Upon examination, the patient was found to have multiple, diffuse soft-tissue lesions measuring 1-5 cm in diameter located throughout his body, in addition to diffuse pigmented macules of 2-4 cm in diameter on the skin. A rough-bordered mass of

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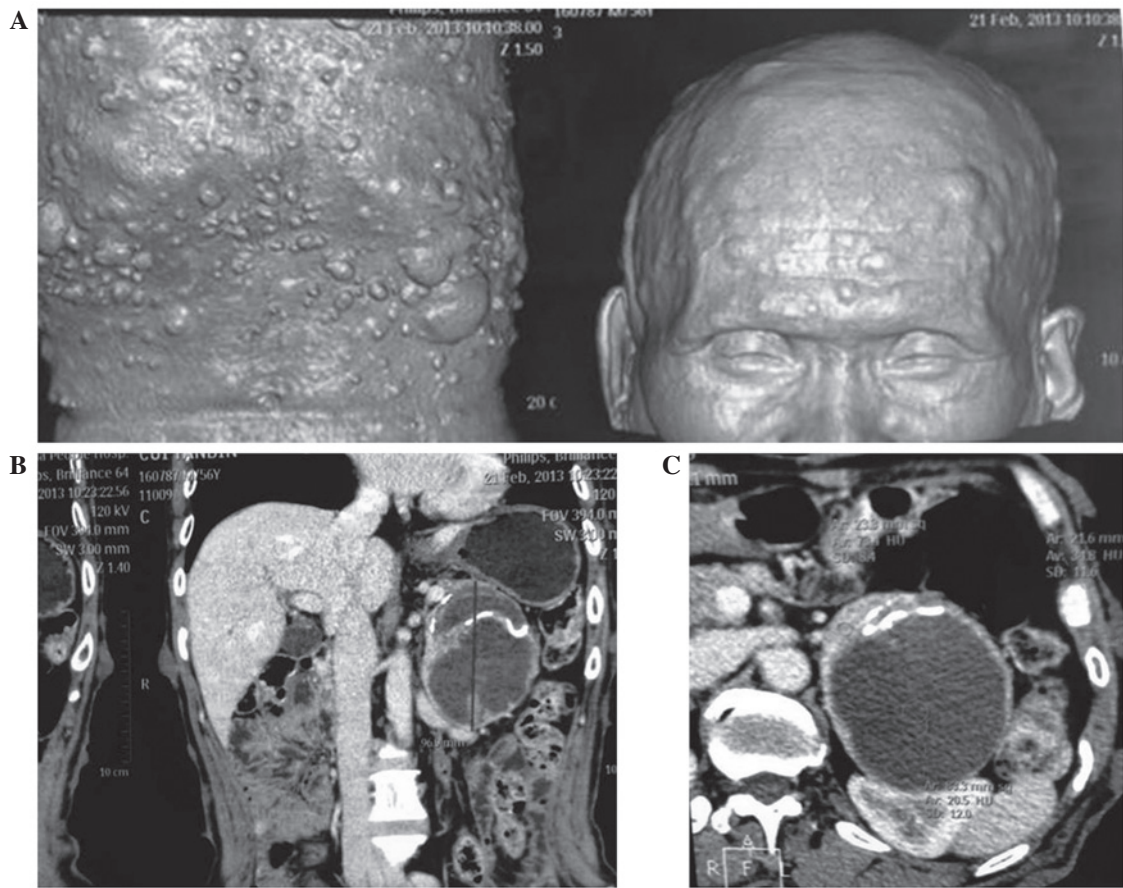


Figure 1. Computed tomography scans of the thorax, abdomen and skull. (A) Multiple nodules with soft tissue density in subcutaneous tissue of abdomen and under the scalp. (B) An oval cystic mass measuring 7.0x7.7x8.9 cm in the left upper abdominal cavity (sagittal view) with capsule wall showing obvious reinforcement; (C) oval cystic mass (axial view).

10x15 cm diameter was palpable in the upper left abdomen, and percussion pain was reported in left kidney area. No optic atrophy, papillary edema or iris Lisch nodules were found in the fundus oculi. The patient had a history of paroxysmal hypertension (up to 220/130 mmHg) for >10 years. In addition, his brother had a history of NF1. Digital radiographic imaging revealed thoracic scoliosis, whilst computed tomography (CT) imaging (performed using a Diamond Select Brilliance CT 16-slice scanner; Philips Medical Systems B.V., Eindhoven, The Netherlands) indicated multiple nodules with soft tissue density, as well as masses under the scalp and subcutaneous tissue of the abdomen (Fig. 1A), and an oval-shaped cystic mass measuring 7.0x7.7x8.9 cm in the left upper abdominal cavity (Fig. 1B and C).

The patient underwent surgical excision of the abdominal tumor, small intestine tumor and part of the subcutaneous nodules for pathological diagnosis. Intraoperative blood pressure fluctuated significantly and peaked at 300/110 mmHg. Postoperative blood pressure remained stable at 140/90 mmHg. Routine anti-infection and intravenous fluid therapy were administered following surgery. For histopathological examination, specimens were fixed with 10% formalin, embedded in paraffin and stained with hematoxylin and eosin (H&E). H&E staining of the abdominal and trunk subcutaneous nodules indicated that the tumor was composed of loose spindle cells, with little, lightly

stained cytoplasm, and thin, wavy nuclei, and the cells were embedded in a fiber-like matrix (Fig. 2A).

The resected tumor from the adrenal gland was grey-red and measured 7.0x7.8x9.0 cm in size. H&E staining of the resected tumor revealed that the tumor capsule was calcified and the tumor contained areas of hemorrhage, necrosis and cholesterol clefts. The tumor cells in areas without hemorrhage and necrosis were arranged in an organoid pattern, with rich vascularity; the cells were moderately abnormal. (Fig. 2B). For immunohistochemical analysis, sections were incubated with antibodies for cluster of differentiation (CD)117 (polyclonal rabbit anti-human; dilution, 1:50; #A4502), S-100 (polyclonal rabbit anti-human; dilution, 1:4,000; #Z0311), Ki-67 (monoclonal rabbit anti-human; dilution, 1:200; #7240), synaptophysin (polyclonal rabbit anti-human; dilution, 1:200; #A010), chromogranin A (polyclonal rabbit anti-human; dilution, 1:500; #A0430), neuron-specific enolase, cyto-keratin (CK)7 (polyclonal rabbit; dilution, 1:500; #A0575) and carcinoembryonic antigen (polyclonal rabbit anti-human; dilution, 1:500; #M7072) for 24 h at 37°C (all purchased from Dako, Glostrup, Denmark). The immunohistochemical findings were S-100 (++) , synaptophysin (++) , chromogranin A (-), neuron-specific enolase (-), CK7 (-), carcinoembryonic antigen (-), Ki-67 (-), p53 (-) and CK18 (-).

The resected small intestine tumor was gray-white and measured 1.3x1.3x1.0 cm. Upon H&E staining, the spindle



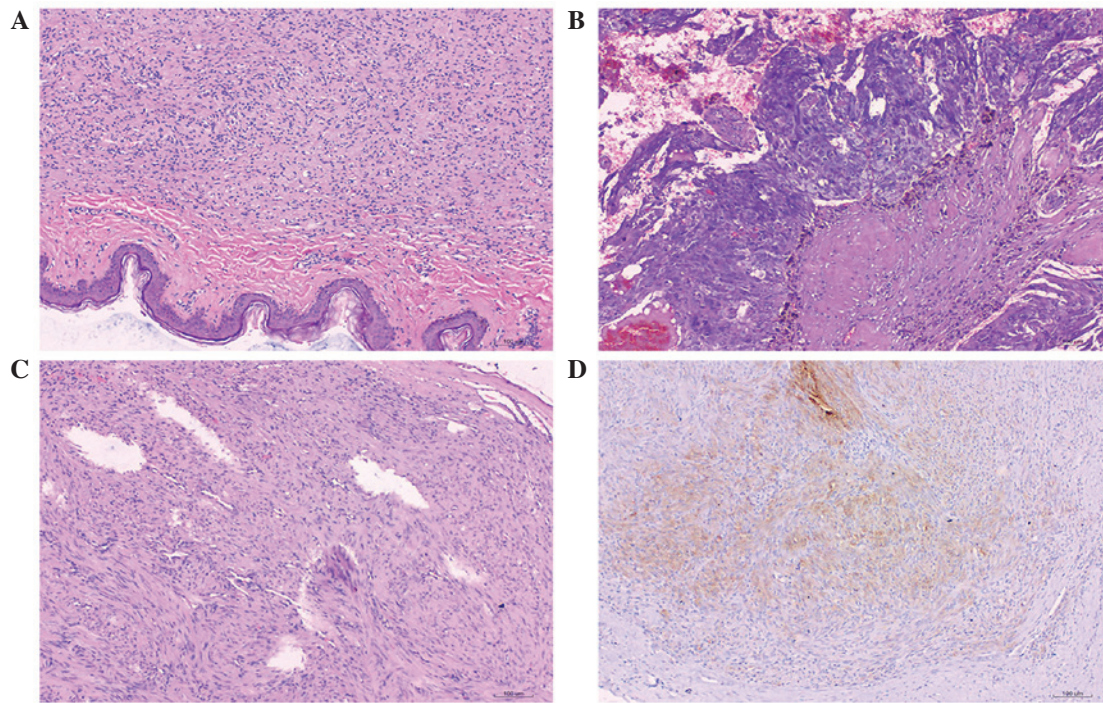


Figure 2. Histological findings (hematoxylin and eosin staining; magnification, x100). (A) Neurofibroma presented as loose spindle cells, with little and lightly stained cytoplasm, thin and wavy nuclei, and cells embedded in a fiber-like matrix. (B) Pheochromocytoma cells were multipolar, with abundant, basophilic cytoplasm and obvious nucleoli; cells were arranged in nest-like or alveolar structures and contained ample vascular fibrous tissue. (C) Small intestine tumors: Spindle cells in stomach muscularis were arranged in bundles, and the nuclei were surrounded by vacuoles. (D) Immunohistochemical staining of small intestine tumors: CD117 (++) was observed in the majority of cells, with the cytoplasm and cell membrane appearing tan colored.

cells in the stomach muscularis were found to be arranged in bundles, and the nuclei were surrounded by vacuoles (Fig. 2C). Immunohistochemical staining showed S-100 (-), CD117 (++) , CD34 (++) , smooth muscle actin (++) and Ki-67 (-) (Fig. 2D). Combining the clinical and pathological findings, the patient was diagnosed with NF1, giant PHEO and small intestinal stromal tumor.

During the one-year postoperative follow-up, the blood pressure of the patient remained in the normal range, and the skin nodules softened and reduced in size. No abnormal lesions were detected in abdominal CT imaging at 6 months post-surgery, and during a 2-year telephone follow-up, the patient stated that they had not experienced abnormal blood pressure or other anomalies. Written informed consent for publication of personal and medical information were obtained from the patient.

## Discussion

The present study conducted a literature search for relevant articles using Pubmed (January 1950 to October 2014), OVID (1951 to October 2014), and Web of Science (1900 to October 2014). To minimize the chance of missing an important study, a manual search of the references of all articles found in our search was also performed, including any potentially eligible studies that were found using Google Scholar. The keywords were as follows: 'Neurofibromatosis', 'pheochromocytoma' and 'gastrointestinal stromal tumors'. As shown in Table I, in addition to the current patient, only 11 similar cases involving a coincidence of GIST and PHEO in NF1 have been published worldwide (9-17). A total of 10 cases

reported the position of PHEO, in which 5 cases occurred in the bilateral adrenal gland; 11 cases reported the position of GISTs, in which 10 cases were located along the small intestine and 2 case was malignant; 8 cases reported clinical features, in which 6 patients had a history of hypertension, 1 patient had melena, 1 had chest pain and 1 had respiratory insufficiency; 7 cases reported clinical outcomes, in which 3 patients succumbed to pulmonary embolism, respiratory insufficiency or intestinal ischemic necrosis, respectively. NF1 is associated with a defect in the *NF1* gene, a tumor suppressor gene located on chromosome 17q11.2. *NF1* encodes neurofibromin, which is responsible for inhibiting the activity of the p21 Ras protein, and induces a variety of clinical manifestations (18). Due to a lack of obvious mutation hotspots, clinical diagnosis of NF1 is still determined based on the criteria of the National Institutes of Health Consensus Development Conference, 1987 (19), which is documented in Table II.

NF1 has a wide range of clinical characteristics (2). The presence of multiple *café au lait* spots and peripheral nerve neurofibromas are prominent features. NF1 is also characterized by several developmental abnormalities, including an increased frequency of benign and malignant tumors. A descriptive analysis based on the international database of the National Neurofibromatosis Foundation (20) suggested that 4.9% of NF1 cases (n=72/1,479) are complicated by other system tumors. Other studies have suggested that 0.1-5.7% of NF1 patients have PHEO (4), whilst 4-25% of patients may have NF1 with GIST (6,7). Thus, the occurrence of PHEO and GIST is rare in patients with NF1.

In a study by Zinnamosca *et al* (21) of 48 patients with NF-1-related PHEO (NF1-PHEO) and an average age of

Table I. Cases with the coincidence of gastrointestinal stromal tumors and pheochromocytoma in neurofibromatosis type 1.

Author, year	Location	Patient gender/ age, years	Position and size of tumors	Previous medical and family history	Clinical manifestation	Laboratory findings <sup>a</sup>	Immunohistochemical staining results	Outcome	Ref.
Vlenterie <i>et al</i> , 2013 <sup>b</sup>	Netherlands	F/59	Left adrenal gland, stomach and small intestine	-	-	-	-	Succumbed to pulmonary embolism	(9)
Vlenterie <i>et al</i> , 2013 <sup>b</sup>	Netherlands	M/55	Bilateral adrenal gland, jejunum	-	-	-	-	Survived	(9)
Ozcinar <i>et al</i> , 2013	Turkey	M/48	Right adrenal gland (2.2 cm), small intestine (1.5-3.5 cm)	Hypertension	Melena, nodule in subcutaneous tissue, <i>café au lait</i> spots	VMA, 9.13 (1.4-6.6) mg/24 h; normetanephrine, 598 (105-354) $\mu$ g/24 h; metanephrine, 1,315 (140-785) $\mu$ g/24 h	CD34 (+), c-Kit (+), CD117 (+), SMA (+), desmin (-), S100 (+), Ki-67 (2%)	NA	(10)
Kramer <i>et al</i> , 2007	Germany	F/63	Left adrenal gland (5 cm), right adrenal gland (3 cm), ileum (6.5 cm), jejunum (3 cm)	Nodule in subcutaneous tissue for 13 years	NA	VMA mildly increased; hormone levels normal	Adrenal gland: S100 (+) GIST: CD34 (+), S100 (-), SMA (-), MIB-1 (2%)	NA	(11)
Teramoto <i>et al</i> , 2007	Japan	F/60	Left adrenal gland (3 cm), small intestine (0.5-2 cm)	Hypertension	Headache, nausea	Blood/urine levels of catecholamines increased	CD34 (+), CD117 (+)	Survived	(12)
Teramoto <i>et al</i> , 2007	Japan	F/67	Bilateral adrenal gland, descending colon (3 cm)	Hashimoto's disease, intestinal polyp, hypertension	Hypertension	Blood/urine levels of catecholamines increased	CD34 (+), CD117 (+)	Succumbed to intestinal ischemic necrosis	(12)
Bümming <i>et al</i> , 2006	Sweden	M/64	Left adrenal gland (6x5 cm), small intestine and mesentery 2-4 cm	Coronary heart disease, hypertension	Intermittent hypertension	Adrenaline (urine level), 13,000 (<101) nmol/24 h, noradrenaline, 15,000 (<551) nmol/24 h; OMC, 72 (<7) nmol/24 h; VMA, 650 (<34) nmol/24 h; plasma CgA, 400 (<45) U/l	Ki-67 (<1%), S100 (+), SMA (-), CD117 (+)	NA	(13)
Lou <i>et al</i> , 2006	China	F/56	Right adrenal gland (4x3x2.5 cm), jejunum (3-5.5 cm)	Nodule in subcutaneous tissue for 50 years, hypertension	Abdominal mass	NA	S100 (+), CD117 (+), CD34 (+) vimentin (+), NSE (+), CgA (+), Syn (+), SMA (-), Bcl (-), KP-1 (-), CK (-)	Survived	(14)

Table I. Continued.

Author, year	Location	Patient gender/ age, years	Position and size of tumors	Previous medical and family history	Clinical manifestation	Laboratory findings <sup>a</sup>	Immunohistochemical staining results	Outcome	Ref.
Jeong <i>et al.</i> , 2005 <sup>b</sup>	Korea	-	-	-	-	-	S100 (+), CD117 (+)	-	(15)
Rizzo <i>et al.</i> , 2000 <sup>b</sup>	Italy	M/60	Bilateral adrenal gland, duodenum, jejunum	-	-	-	-	-	(16)
Sakaguchi <i>et al.</i> 1996	Japan	M/48	Bilateral adrenal gland, gastrointestinal tract (malignant)	NA	Chest pain, paroxysmal hypertension, respiratory insufficiency	NA	NA	Succumbed to respiratory insufficiency	(17)

<sup>a</sup>Values in brackets indicate normal reference ranges of laboratory markers. <sup>b</sup>Abstracts were used. F, female; M, male; NA, not reported; VMA, vanillylmandelic acid; OMC, methoxycatecholamines; CD, cluster of differentiation; SMA, smooth muscle actin; GIST, gastrointestinal stromal tumor; NSE, neuron-specific enolase; CgA, chromogranin A; Syn, synaptophysin; Bel, B-cell lymphoma; CK, cytokeratins.

Table II. Diagnostic criteria for NF1.

No.	Description
1	Six or more <i>café au lait</i> spots measuring $\geq 5$ mm in diameter in prepubertal individuals or $\geq 15$ mm in diameter in postpubertal individuals
2	Two or more neurofibromas of any type, or one plexiform neurofibroma
3	Freckling in the axillary or inguinal regions
4	Optic glioma
5	Two or more Lisch nodules (iris hamartomas)
6	A distinctive osseous lesion, such as sphenoid dysplasia or thinning of long bone cortex, with or without pseudoarthrosis
7	A first degree relative (parent, sibling or offspring) with NF1 based on the above criteria

The patient should have two or more of the criteria for diagnosis. NF1, neurofibromatosis type 1.



39 years, ~85% of patients had single adrenal tumors, whilst 15% had bilateral adrenal tumors. In addition, 57% of patients exhibited the clinical features of high catecholamine concentration, including headache, heart palpitations, sweating and hypertension. In previous reports of clinical cases, paroxysmal hypertension was observed in the majority of NF1-PHEO patients; these results suggest that the periodic evaluation of NF1 patients with hypertension for the presence of PHEO is necessary (21-24).

The development of PHEO may be associated with the type of *NF1* expression. Gutmann *et al* (25) demonstrated a lack of neurofibromin expression in PHEO from 6 patients with NF1, supporting the idea that neurofibromin may participate in the pathogenesis of NF1-PHEO. Additionally, reduced or absent *NF1* gene expression was documented in a proportion of PHEO patients without NF1. Furthermore, the majority of PHEO cases expressed predominantly the type 1 NF1 isoform (75%), as opposed to the adrenal glands, which express predominantly type 2 NF1 (60%) (25).

The incidence of GIST accounts for only 0.1-3.0% of all gastrointestinal tumors (26); however, 11-25% patients with NF1 also have gastrointestinal carcinoid tumors (27). Although 60% of GISTs occur in the stomach whilst only 20-30% occur in the small intestine (28), NF1-related GISTs (NF1-GIST) tend to be located in the small intestine (28). The pathogenesis of NF1-GIST is different to that of sporadic GIST. The latter, which is widely considered to involve specific KIT (CD117) or platelet-derived growth factor receptor  $\alpha$  polypeptide (PDGFR $\alpha$ ) signaling-driven tumors, is characterized by frequent allelic losses of 1p, 14q and 22q, and mutations of the *KIT* or *PDGFR $\alpha$*  genes (6,29). By contrast, mutations in *KIT* and *PDGFR $\alpha$*  are extremely rare events in NF1-GIST (29). Rather, cell proliferation in NF-1 GIST is associated with the activation of the Ras-mitogen-activated protein kinase pathway, which may be activated via *KIT* or *PDGFR $\alpha$*  in association with the inactivation of the *NF1* gene. Additionally, loss of heterozygosity at 14q and 22q may contribute to the relatively early phase of tumor development of NF1-GIST (30). The diagnosis of GIST primarily depends on the histopathological and immunohistochemical phenotype. One of the main characteristic of GIST is positivity for CD117 and CD34 (31,32). In the majority of the present patients with NF1-GIST, CD117 and CD34 were positive, which is conducive to confirming a diagnosis.

Surgical removal is the only definitive therapy for PHEO (33). However, it is important to note that patients who experience an inconspicuous intraoperative blood pressure drop or rapid recovery of previously low blood pressure during tumor excision have the possibility for residual tumor or metastases (33). Thus, careful monitoring of blood pressure should be conducted during surgery. In addition, surgical excision is the standard approach for GIST of >2 cm in diameter or with nuclear pleomorphism as a histological feature (34). Treatment should be supplemented with imatinib mesylate for suppression of CD117 receptors and prevention of tumor recurrence or metastasis (35).

In conclusion, the current study reiterates that cases of NF1 occurring with PHEO and GIST are rare. The clinical symptoms of these cases varied; however, paroxysmal hypertension occurred in the majority of patients, and GISTs were largely located in the small intestine. The present study aims to offer guidance in the diagnosis and treatment of similar cases.

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