Neuroendocrinology Letters Volume 46 No. 2 2025
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

CASE REPORT

A Rare Case: Composite Paraganglioma-Ganglioneuroma in a Neurofibromatosis 1 Patient and Literature Review

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Submitted: 2024-11-16 *Accepted: 2025-08-08* *Published online: 2025-08-26*

Key words: **Paraganglioma; Ganglioneuroma; Neurofibromatosis 1; Mutation; Neuroendocrine tumors**

Neuroendocrinol Lett 2025; **46**(2):70–76 **PMID:** 40929705 46022501

Abstract

BACKGROUND: Pheochromocytomas and paragangliomas (PPGLs) are rare catecholamine-secreting neuroendocrine tumors originating from the embryonic neural crest. Approximately 30% of PPGLs are hereditary and are frequently associated with genetic syndromes, including neurofibromatosis type 1 (NF1). Composite PPGLs, which include components of both PPGLs and related tumors such as ganglioneuromas, are extremely rare in NF1 patients.

CASE PRESENTATION: A 40-year-old woman with NF1, identified by multiple neurofibromas, café-au-lait spots, axillary freckling, and Lisch nodules, presented with an incidental mass adjacent to the right adrenal gland. Computed tomography and magnetic resonance imaging revealed a possible PPGL, with additional small nodules suspected to be gastrointestinal stromal tumors or neuroendocrine tumors. Genetic testing revealed a heterozygous *NF1* gene mutation, c.2786T>C. The patient underwent successful robotic-assisted laparotomy to remove a 5 cm retroperitoneal tumor. Pathological examination revealed a composite paraganglioma-ganglioneuroma. The patient recovered well postoperatively and was recommended for long-term follow-up.

CONCLUSION: This report describes the first Chinese case of composite extra-adrenal paraganglioma-ganglioneuroma in an NF1 patient, highlighting the importance of a multidisciplinary approach, including genetic analysis, for the accurate diagnosis and management of composite PGLs in NF1 patients. This unique case underscores the clinical significance of recognizing rare composite tumors in diverse populations to improve diagnosis and personalized treatment strategies. Further research into the genetic and clinical implications of these tumors is important.

Abbreviations & units:

PGL - Paraganglioma;
PCC - Pheochromocytoma;
PPGL - Pheochromocytomas and paraganglioma;
GIST - gastrointestinal stromal tumor;
NET - Neuroendocrine tumor;
NF1 - Neurofibromatosis 1;
CT - Computed tomography;
MR - Magnetic resonance;
NSE - Neuron-specific enolase;
Syn - Synaptophysin;
GN - Ganglioneuroma.
SDH - Succinate dehydrogenase
RET - Rearranged during transfection;
SDHA - Succinate Dehydrogenase Complex Flavoprotein Subunit

INTRODUCTION

Pheochromocytomas and Paragangliomas (PPGLs) are neuroendocrine tumors (NETs) that originate from chromaffin cells within the adrenal medulla and extra-adrenal paraganglia, respectively, with an annual incidence of 0.04 to 0.95 cases per 100,000 individuals (Tevosian & Ghayee 2019; Al Subhi *et al.* 2022). A significant proportion, about 30%, of these tumors have a hereditary basis, typically resulting from autosomal dominant germline mutations. They are frequently associated with hereditary syndromes, including neurofibromatosis 1 (NF1) and multiple endocrine neoplasia Type 2 (MEN2). Paragangliomas (PGLs) in the neck and skull are notably linked to mutations in the succinate dehydrogenase *(SDH)* enzyme complex genes (Neumann *et al.* 2019). Composite PPGLs are characterized by the presence of both typical PPGL elements and components of a neuroblastic tumor, such as ganglioneuroma (GN) or other related neoplasms. These composite tumors are exceptionally rare, with an even rarer association with genetic syndromes or mutations in *SDH* genes (Mete *et al.* 2022).

NF1, an autosomal dominant disorder affecting approximately 1 in 3,000 individuals, presents with symptoms like pigmentary lesions and neurofibromas and can be complicated by skeletal issues and brain tumors (Neumann *et al.* 2019; Al-Sharefi *et al.* 2019). The occurrence of PPGLs in NF1 patients is low, at 1-3%, with composite PGLs being extraordinarily rare within this population. Herein we report the first Chinese NF1 patients with a composite extra-adrenal paraganglioma-ganglioneuroma along with a literature review. We hope to add some valuable perspectives on this rare condition.

CASE PRESENTATION

A 40-year-old woman was admitted to the hospital following an incidental finding of a pancreatic mass on a routine abdominal ultrasound examination. She was asymptomatic, with no reported abdominal pain, nausea, diarrhea, headaches, palpitations, or swelling. The patient had a history of surgery for congenital heart disease 30 years prior. Physical examination revealed a weight of 50.6 kilograms and a height of 150 cm, with normal blood pressure. She exhibited several café-au-lait spots on her trunk, each over 1.5 cm in diameter, along with multiple neurofibromas and axillary freckling. Ophthalmic examination identified Lisch nodules. Her son and daughter also displayed café-au-lait spots, with the son having undergone surgery for scoliosis. A 24-hour Holter monitor showed normal blood pressure readings. An echocardiogram showed an enlarged right ventricle, thinning of the left pulmonary artery, and mild pulmonary artery stenosis.

Abdominal computed tomography (CT) imaging revealed a heterogeneously enhancing retroperitoneal mass, measuring 4.6 × 3.5 cm, adjacent to the medial aspect of the right adrenal gland (Figure 1A). Small hypervascular nodules, 1–1.5 cm in diameter, were also noted between the pancreatic head and the descending duodenum, and within the jejunal wall on the right side, raising suspicion for gastrointestinal stromal tumors (GISTs) or NETs. Magnetic resonance (MR) imaging confirmed a short oval mass, approximately 4 cm in its longest dimension, at the right adrenal junction. The mass showed mixed high and low signals on T2 and diffusion-weighted imaging, and uneven low signals on T1 images. Post-contrast enhancement demonstrated irregular wall thickening, with contrast accumulation in the center during the delayed phase and a few small cystic areas, suggestive of a pheochromocytoma (PCC) or PGL (Figure 1B). An overnight 1 mg-dexamethasone

Tab. 1. Results of plasma metanephrines

	Results	Units	Reference
3-Methoxytyramine	<0.08	nmol/L	<0.18
Metanephrine	0.29	nmol/L	≤0.50
Normetanephrine	3.55	nmol/L	≤0.90
Dopamine	<65.2	pmol/L	Supine and upright ≤605.4
Epinephrine	578.2	pmol/L	Supine ≤605.4; Upright ≤769.0
Norepinephrine	1825.3	pmol/L	Supine 414.0–4435.5; Upright 1182.8–10054.0

Blood samples were collected in the supine position unless otherwise specified. Plasma free metanephrines measurement method was used.

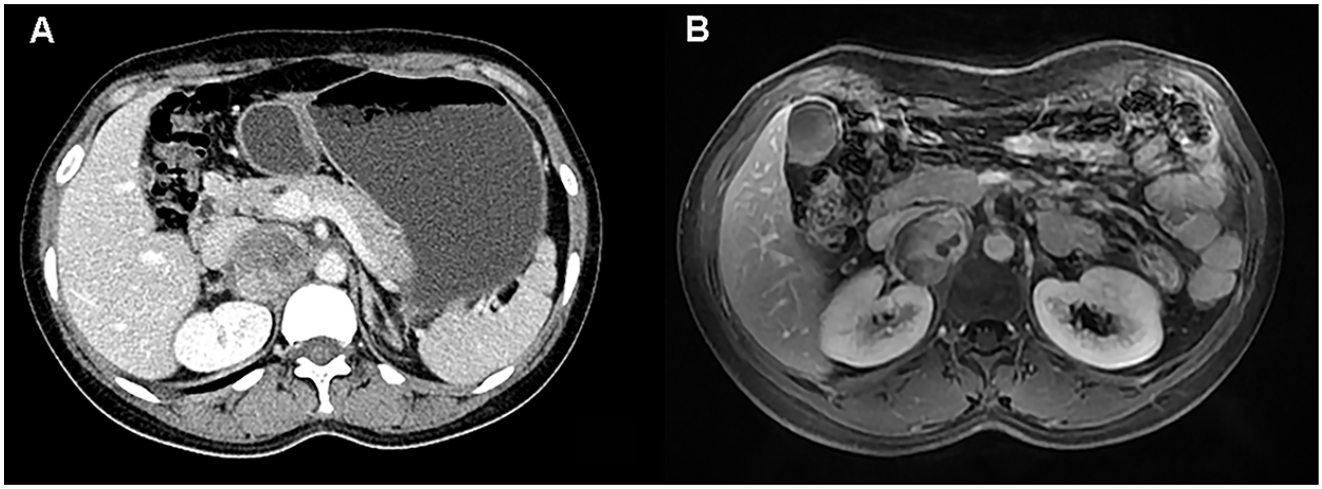

Fig. 1. Radiological imaging of the abdomen.
A. Abdominal CT scan revealed a 4.6 × 3.5 cm heterogeneously enhancing mass adjacent to the right adrenal. B. Contrast-enhanced transaxial T1-weighted MR image revealed a 4 cm heterogeneous right retroperitoneal mass with uneven low signals and internal cystic changes

suppression test ruled out autonomous cortisol secretion. Plasma metanephrines test showed significantly elevated normetanephrine levels, while other hormone levels remained within normal limits (Table 1).

Next-generation sequencing of the entire exome identified a heterozygous mutation, c.2786T>C (p.Leu929Pro), in the *NF1* gene on chromosome 17, confirming the diagnosis of NF1. Sanger sequencing, used for validation, revealed the same mutation in the patient's son. Regrettably, the patient's daughter declined genetic testing.

Following a comprehensive multidisciplinary discussion, it was determined that the patient should undergo surgical resection of a mass located near the right adrenal gland. Preoperative blood pressure management was achieved with terazosin. During the robotic-assisted laparotomy, a 5 cm right retroperitoneal tumor was located. The tumor's superior boundary was in proximity to the renal vessels, its inferior boundary to the psoas major muscle, and it appeared to arise from the lumbar nerve root. Complete resection of the tumor was successfully performed.

Postoperative pathology confirmed a retroperitoneal composite paraganglioma-ganglioneuroma. The patient recovered well postoperatively without any immediate complications, and no adjuvant chemotherapy or radiotherapy was indicated. Routine annual monitoring with plasma metanephrine testing and abdominal MR imaging examination was advised to survey for gastrointestinal nodules and potential paraganglioma recurrences.

PATHOLOGY

The resected tumor, characterized by a distinct capsule and dimensions of 5.2 × 4.7×3 cm, presented a predominantly yellowish hue punctuated by darker areas scattered throughout its surface. Upon microscopic examination, the tumor was revealed to be a complex intermixture of typical paraganglioma regions seamlessly interwoven with ganglioneuroma components (Figure 2).

Immunohistochemical analysis delineated the cellular characteristics of the tumor. The PGL's

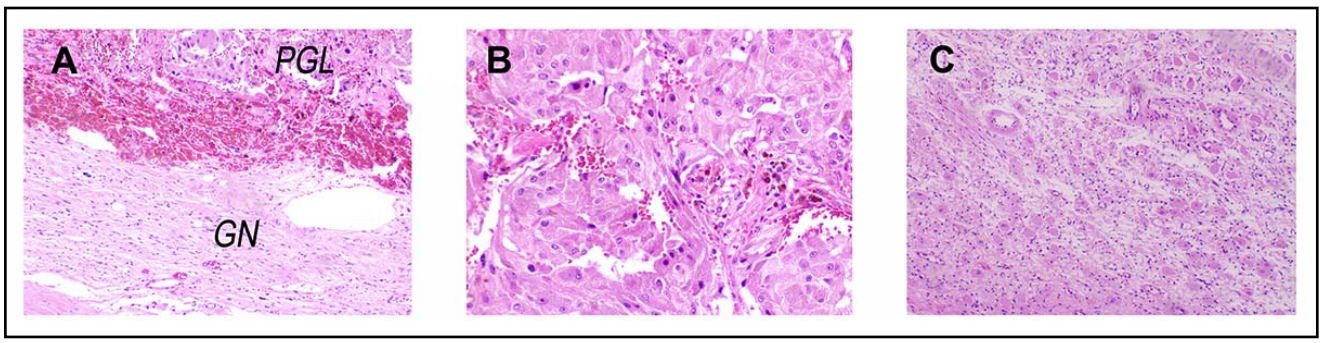

Fig. 2. Pathological findings in the composite tumor
A. Representative images of the tumor and histologic features in the vertical section showing both paraganglioma (PGL) and ganglioneuroma (GN) components observed by H&E staining (×40). B. Paraganglioma component showed classic nested or "zellballen" architecture (H&E staining, ×100). C. Ganglioneuroma component was well-differentiated (H&E staining, ×100).

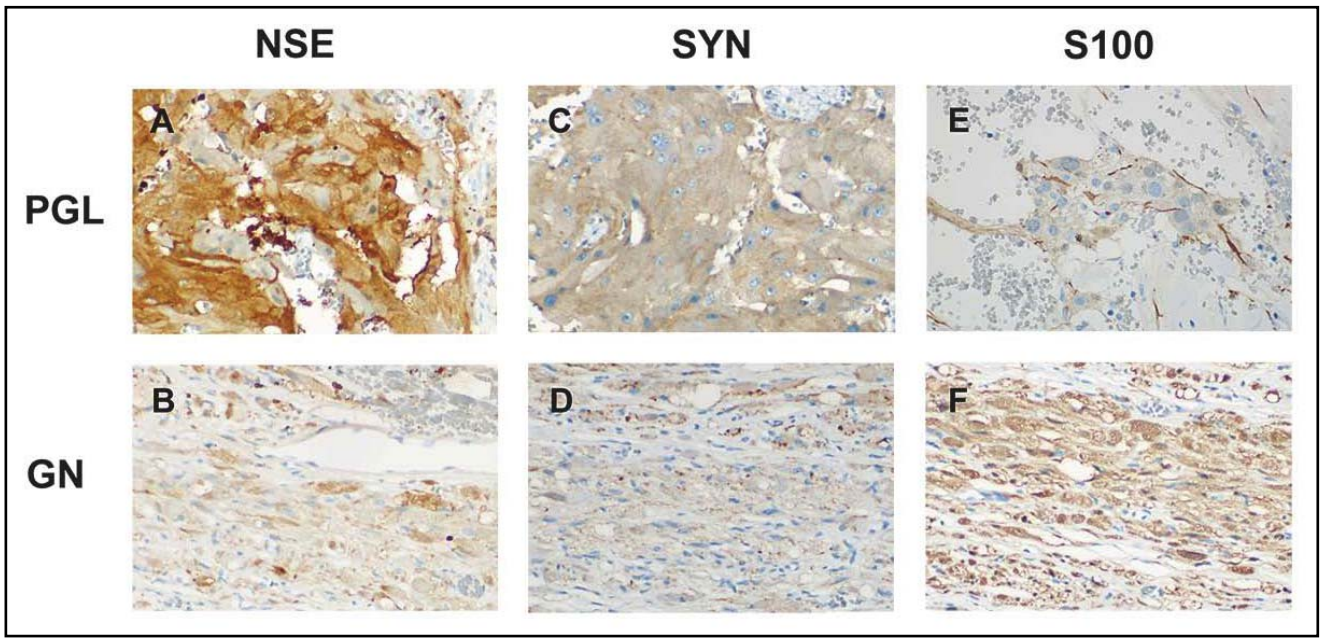

Fig. 3. Immunohistochemical Staining of the composite tumor
Paraganglioma (PGL) component: A. neuron-specific enolase (NSE), C. synaptophysin (Syn), E. S100; Ganglioneuroma (GN) component: B. NSE, D. Syn, F. S100 (×100)

chromaffin cells were strongly positive for neuron-specific enolase (NSE) and synaptophysin (Syn) (Figure 3A & C). In the GN component, ganglion cells also displayed positive staining for NSE and Syn (Figure 3B & 3D). Sustentacular cells in the PGL and Schwannian cells in the GN were identified by their unique S100 staining patterns (Figure 3E & 3F). The Ki-67 labeling index indicated a low proliferation rate of about 1%, suggesting a relatively benign biological behavior.

DISCUSSION

A comprehensive literature review was conducted to identify all previously reported cases of composite paragangliomas, particularly those associated with NF1. The electronic database PubMed was searched up to July 2024 using the following keywords and their combinations: ("composite paraganglioma" OR "composite pheochromocytoma") AND ("ganglioneuroma"), and ("composite paraganglioma" OR "composite pheochromocytoma") AND ("neurofibromatosis 1" OR "NF1").

Based on this search, it was reconfirmed that composite PPGLs are relatively rare, with PCCs being the predominant component in more than 70% of cases(Gupta *et al.* 2017). In a review of 110 composite adrenal PCCs, approximately 20% were associated with genetic predisposition syndromes, notably NF1, which accounted for 15 of these cases (Costa *et al.* 2023). A recent review summarized that only 34 cases of composite PGLs have been documented, highlighting their rarity. Composite PGLs linked to genetic syndromes or SDH mutations are exceedingly uncommon, with only 5 cases including the present one recorded to date, suggesting that the proportion of composite PGLs associated with hereditary syndromes (14.3%) is even lower compared to that of composite PCCs (19.1%).

Table 2 summarized the clinical characteristics of reported composite PGLs with germline mutations. Only three NF1 patients with composite PGLs have been reported until now. These patients typically ranged from 34–40 years of age and two were female. The composite tumors of two patients were located retroperitoneally, and one was located in the pancreas, with sizes varying from 3.0 cm to 6.8 cm. The clinical presentations varied; the patient with pancreatitis was symptomatic and presented with abdominal pain, vomiting, and hypertension, whereas the other two patients were asymptomatic. All three patients exhibited excessive normetanephrine secretion, and the patients with pancreatitis additionally presented elevated norepinephrine and dopamine levels. This finding is consistent with the literature indicating that PGLs usually produce only noradrenaline due to the absence of phenylethanolamine N-methyltransferase expression (Patel *et al.* 2020). In our patient, despite the absence of hypertension, tests for plasma metanephrines revealed significantly elevated normetanephrine levels, underscoring the importance of biochemical testing in detecting underlying biochemical activity even in asymptomatic individuals. Another notable feature of all identified composite PGLs with genetic syndromes was the presence of ganglioneuroma (GN) components. GN is a benign tumor that consists of mature ganglion cells and Schwannian stroma. In a study by Sasaki *et al.* 34 composite PGLs were reported, of which 29 contained

Tab. 2. Literature Review of Composite Paraganglioma in Syndromic Patients

Age /Sex	Clinical Features	Tumor Location	Tumor Size (cm)	Other presentations	Syndrome	Gene Abnormality	Hormone Excess	Family History	Follow-up	Year, Nation
34/F	Abdominal pain, vomiting, Hypertension	Pancreas	6.8×4.9×4.6	Neck plexiform neurofibromas(NFs) on neck; Facial, retroperitoneal and mediastinal freckles; Café-au-lait spots on trunk and extremities.	Neurofibromatosis type 1(NF1)	Not applicable (NA)	Normeta-nephrine (NM)	NA	NA	2012, USA (Majumder *et al.* 2012)
67/M	NA	Retroperitoneum	6.2	NA	NF1	NA	Norepine -phrine/NM +Dopamine	NA	Tumor-free for 7 months after surgery	2017, USA (Gupta *et al.* 2017)
40/F	None	Retroperitoneum	5.2×4.7×3	Facial and trunk NFs Café-au-lait spots on truck; Lisch nodules; Freckles; Gastrointestinal stromal tumors in duodenum and jejunum	NF1	Heterozygous p.Leu929Pro mutation in NF1 gene	NM	Son	NA	China (present)
59/M	Paroxysmal hypertension	Retroperitoneum	3	Adrenal metastasis of medullary thyroid carcinoma	Multiple endocrine neoplasm 2B	M918T germline mutation in RET gene	Metanephrine+Vanillylman -delic acid.	NA	NA	2017, Japan (Yamasaki *et al.* 2017)
50/F	Hypertension	Right carotid space	5.9×1.2× 0.5	Diabetes mellitus; osteoarthritis; infertility	Paraganglioma syndrome	Heterozygous SDHA c.691dupT loss-of-function mutation	Normal	NA	NA	2019, USA (Delgado *et al.* 2019)

NA, not available; NF: neurofibroma; NF1: neurofibromatosis type 1; NM, normetanephrine; RET: Rearranged during transfection; SDHA: Succinate Dehydrogenase Complex Flavoprotein Subunit A

GN components, three included neuroblastoma components, and two had ganglioneuroblastoma components (Sasaki *et al.* 2024). The reason why most of composite PGLs contain GN component is unclear, and warrants further investigation.

Mutations in the *NF1* gene are uncommon in PPGLs, occurring in about 1.6% of incidental and 2.7% of nonincidental cases within the Chinese population (Zhang *et al.* 2022). The *NF1* gene, situated on chromosome 17q11.2, encodes the tumor suppressor protein neurofibromin, which acts as a negative regulator of the *Ras/MAPK* and *PI3K/mTOR* signaling pathways (Tamura 2021). Patients with *NF1* gene mutations typically exhibit a range of clinical features, such as neurofibromas, Lisch nodules, and café-au-lait spots, similar to the manifestations observed in our patient. Unfortunately, in the two previously published cases of composite PGLs associated with NF1 patients, no results of genetic analysis were reported. In our case, genetic analysis revealed a heterozygous missense mutation in the *NF1* gene on chromosome 17, c.2786T>C (p.Leu929Pro), which has been previously reported among NF1 patients (Koczkowska *et al.* 2018; Ribeiro *et al.* 2012; Violante *et al.* 2013). The same mutation was identified in her son, who also presented with relevant clinical features, indicating the heritability of this mutation. However, there are no current data on the prevalence of this mutation in the general East Asian population. Notably, in the other three reported NF1 cases with this mutation, none have been linked to PPGLs, suggesting that the association between this *NF1* mutation and the development of composite PPGLs is not well established and merits further research.

Lastly, the successful surgical management of this patient and the recommendation for close surveillance with plasma metanephrine testing and abdominal MR imaging examination highlighted the importance of a multidisciplinary approach to the management of composite PPGLs. The decision to forego adjuvant therapy in this patient was based on the low Ki-67 index, suggesting a relatively benign biological behavior. However, the potential for recurrence and the need for long-term follow-up cannot be overlooked. Besides, there were also some shortcomings in our treatment. Due to the lack of functional imaging technologies for NETs, for instance scintigraphy with ^{123}I-labeled metaiodobenzylguanidine, it was not possible to further determine whether the small nodules in the gastrointestinal tract were NETs or not.

CONCLUSION

In this case, the diagnosis of composite extra-adrenal paraganglioma-ganglioneuroma in the context of NF1 was confirmed through imaging, biochemical testing, pathological examinations and genetic analysis. This case emphasizes the importance of a multidisciplinary approach, including genetic counseling, for the management of such rare tumors. The identification of the *NF1* gene mutation, c.2786T>C, in the patient and her son, along with the atypical presentation and the tumor's composite nature, underscores the need for further research into the genetic factors and molecular mechanisms contributing to the development of PPGLs in NF1 patients. The patient's favorable outcome following surgery and the decision to monitor without adjuvant chemotherapy highlight the individualized treatment strategy that can be employed in such cases.

FUNDING

This work was supported by the Principal Foundation of Tarim University (TDZKCX202511).

ETHICS APPROVAL

This study was approved by the Medical Ethics Committee of Sir Run Run Shaw Hospital, Zhejiang University School of Medicine.

ACKNOWLEDGMENTS

None.

CONFLICTS OF INTEREST

The authors declared that there were no conflicts of interest associated with this manuscript.

REFERENCES

1 Al-Sharefi A, Javaid U, Perros P, Ealing J, Truran P, Nag S, Kamaruddin S, Abouglila K, et al. (2019). Clinical Presentation and Outcomes of Phaeochromocytomas/Paragangliomas in Neurofibromatosis Type 1. Eur Endocrinol. **15**: 95–100.
2 Al Subhi AR, Boyle V, Elston MS (2022). Systematic Review: Incidence of Pheochromocytoma and Paraganglioma Over 70 Years. J Endocr Soc. **6**: bvac105.
3 Costa J, Jácome M, Souteiro P, Santos C, Cunha AL (2023). Composite pheochromocytoma of the adrenal gland-a review of published cases. Virchows Arch. **483**: 267–275.
4 Delgado S, Smith SM, Mehra S, Prasad ML (2019). Composite Paraganglioma: Pioneering in the Head and Neck. Int J Surg Pathol. **27**: 282–289.
5 Gupta S, Zhang J, Erickson LA (2017). Composite Pheochromocytoma/Paraganglioma-Ganglioneuroma: A Clinicopathologic Study of Eight Cases with Analysis of Succinate Dehydrogenase. Endocr Pathol. **28**: 269–275.
6 Koczkowska M, Chen Y, Callens T, Gomes A, Sharp A, Johnson S, Hsiao MC, Chen Z, et al. (2018). Genotype-Phenotype Correlation in NF1: Evidence for a More Severe Phenotype Associated with Missense Mutations Affecting NF1 Codons 844–848. Am J Hum Genet. **102**: 69–87.
7 Majumder S, Grabska J, Trikudanathan G, Kowalczyk P, Stoica-Mustafa E, Dasanu CA (2012). Functional 'composite' pheochromocytoma-ganglioneuroma presenting as a pancreatic mass. Pancreatology. **12**: 211–214.
8 Mete O, Asa SL, Gill AJ, Kimura N, De Krijger RR, Tischler A (2022). Overview of the 2022 WHO Classification of Paragangliomas and Pheochromocytomas. Endocr Pathol. **33**: 90–114.
9 Neumann HPH, Young WF, Jr., Eng C (2019). Pheochromocytoma and Paraganglioma. N Engl J Med. **381**: 552–565.

10 Patel D, Phay JE, Yen TW, Dickson PV, Wang TS, Garcia R, Yang AD, Solórzano CC, et al. (2020). Update on pheochromocytoma and paraganglioma from the SSO endocrine/head and neck disease-site work group. Part 1 of 2: advances in pathogenesis and diagnosis of pheochromocytoma and paraganglioma. Annals of surgical oncology. **27**: 1329–1337.
11 Ribeiro MJ, Violante IR, Bernardino I, Ramos F, Saraiva J, Reviriego P, Upadhyaya M, Silva ED, et al. (2012). Abnormal achromatic and chromatic contrast sensitivity in neurofibromatosis type 1. Invest Ophthalmol Vis Sci. **53**: 287–293.
12 Sasaki Y, Kanzawa M, Yamamoto M, Kanie K, Bando H, Yoshino K, Hirota Y, Shigemura K, et al. (2024). Composite paraganglioma-ganglioneuroma with atypical catecholamine profile and phenylethanolamine N-methyltransferase expression: a case report and literature review. Endocrine Journal. **71**: 65–74.
13 Tamura R (2021). Current Understanding of Neurofibromatosis Type 1, 2, and Schwannomatosis. Int J Mol Sci. **22**: 5850.
14 Tevosian SG, Ghayee HK (2019). Pheochromocytomas and Paragangliomas. Endocrinol Metab Clin North Am. **48**: 727–750.
15 Violante IR, Ribeiro MJ, Edden RA, Guimaraes P, Bernardino I, Rebola J, Cunha G, Silva E, et al. (2013). GABA deficit in the visual cortex of patients with neurofibromatosis type 1: genotype-phenotype correlations and functional impact. Brain. **136**: 918–925.
16 Yamasaki M, Sato Y, Nomura T, Sato F, Uchino S, Mimata H (2017). Composite paraganglioma-ganglioneuroma concomitant with adrenal metastasis of medullary thyroid carcinoma in a patient with multiple endocrine neoplasia type 2B: A case report. Asian J Endosc Surg. **10**: 66–69.
17 Zhang J, Li M, Pang Y, Wang C, Wu J, Cheng Z, Li X, Lu Z, et al. (2022). Genetic Characteristics of Incidental Pheochromocytoma and Paraganglioma. J Clin Endocrinol Metab. **107**: e1835-e1842.