

# Concurrent primary hyperparathyroidism and pheochromocytoma in a Chinese lady with neurofibromatosis type 1

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## Summary

We report a case of elderly Chinese lady with neurofibromatosis type-1 presenting with longstanding palpitation, paroxysmal hypertension and osteoporosis. Biochemical testing showed mild hypercalcaemia with non-suppressed parathyroid hormone level suggestive of primary hyperparathyroidism, and mildly elevated urinary fractionated normetanephrine and plasma-free normetanephrine pointing to a catecholamine-secreting pheochromocytoma/paraganglioma. Further scintigraphic investigation revealed evidence of a solitary parathyroid adenoma causing primary hyperparathyroidism and a left pheochromocytoma. Resection of the parathyroid adenoma and pheochromocytoma resulted in normalization of biochemical abnormalities and hypertension. The rare concurrence of primary hyperparathyroidism and pheochromocytoma in neurofibromatosis type-1 is discussed.

## Learning points:

- All NF-1 patients who have symptoms suggestive of a pheochromocytoma/paraganglioma (PPGL), even remotely, should undergo biochemical testing.
- The initial biochemical tests of choice for PPGL in NF-1 are either plasma-free metanephrines or urinary fractionated metanephrines. Any elevations of metanephrines should be carefully evaluated for the presence of PPGLs in NF-1 patients.
- Primary hyperparathyroidism (PHPT) is described in subjects with NF-1. Due to the lack of epidemiological and functional studies, their association is yet to be substantiated. Meanwhile, PHPT may further exacerbate the metabolic bone defect in these patients and should be treated when present according to published guidelines.
- Coexistence of PPGL and PHPT can occur in subjects with NF-1, mimicking multiple endocrine neoplasia type 2 (MEN2).

## Background

Neurofibromatosis type-1 (NF-1) is a dominantly inherited genetic disorder with age-dependent penetrance and highly variable expressivity (1). The causative gene *NF1*, located in 17q11.2, is a tumour suppressor gene, which encodes neurofibromin. Neurofibromin negatively regulates RAS by converting it from the active GTP-bound form to the inactive GDP-bound form (2). Loss

of neurofibromin results in hyperactivation of the RAS proto-oncogene, which is a key signalling molecule of cell growth. Therefore, NF-1 is now recognized as a form of RASopathy, where dysregulated RAS-MAPK signalling pathway causes cancer predisposition (3). Pheochromocytoma/paraganglioma (PPGL) is one of the most common endocrine neoplasia associated with NF-1

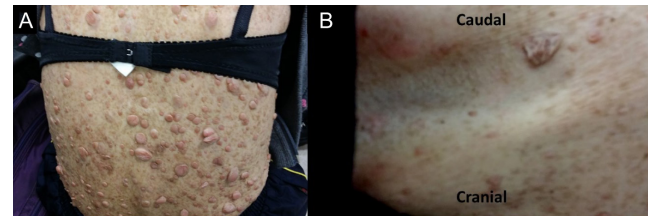


and is observed in 0.1–14% of patients with NF-1 (4, 5, 6, 7). On the other hand, primary hyperparathyroidism has only been rarely reported as isolated cases and the majority is due to the presence of solitary parathyroid adenoma (8). Coexistence of pheochromocytoma and primary hyperparathyroidism (PHPT) was exceptional and may be mistaken as multiple endocrine neoplasia type 2 (MEN2). Clinicians should therefore remain vigilant of these endocrine manifestations and investigate for them especially in symptomatic patients.

## Case presentation

A 65-year-old Chinese lady presented to our unit for palpitation for several years. She had been diagnosed with neurofibromatosis type 1 clinically since teenage. Her past medical history was notable for hyperlipidemia, osteoporosis and white coat hypertension. Her family history was notable for NF-1 in her daughter and son as well.

She first experienced on and off palpitation back in the year 2010. She described it as a fast, regular thumping sensation over the precordium which was mostly short-living and lasted no more than five to ten minutes. The symptom was worse when she had exertion and felt anxious. It was not associated with chest pain, dyspnoea, dizziness, sweating or pallor. Neither was there any precipitating factor. The symptom of palpitation was relatively mild initially and did not cause much impairment in her daily living. As a result, the patient did



**Figure 1**

(A) Multiple cutaneous neurofibromata at the back of the patient. (B) Multiple axillary freckles over right armpit. (Pictures were taken with courtesy of our patient).

not seek medical advice till year 2013 when the paroxysms of palpitation became more troublesome.

Upon physical examination, the patient had multiple cutaneous neurofibromata over trunk and limbs, numerous café-au-lait spots and bilateral axillary freckling (Fig. 1). There was also presence of Lisch nodules bilaterally. Goitre was not present, and there was no sign of hyperthyroidism. Cardiovascular, respiratory and neurological examinations were all unremarkable. Office blood pressure was in the range of 130–160mmHg for systolic blood pressure and 75–90mmHg for diastolic blood pressure. Baseline ECG showed normal sinus rhythm. TSH and free T4 were normal. A 24-h Holter examination was performed, and apart from occasional supraventricular and ventricular ectopics (<0.5%), no significant arrhythmia was detected. A 24-h urinary examination on catecholamines was normal in May 2014 (Table 1). The symptom of palpitation was initially attributed to anxiety.

**Table 1** Biochemical testing of patient.

Tests	May 2014	May 2015	Dec 2015	Sep 2016	Reference ranges
Calcium mmol/L	<b>2.64</b>				2.24–2.63
Phosphate mmol/L	0.94				0.88–1.45
Albumin g/L	39				38–48
24 h urine calcium mmol/24 h	4.69				2.5–7.5
PTH pmol/L	<b>12</b>				1.1–7.3
24-h urinary FC and MN					
NE nmol/24 h	<b>328*</b>	<b>475#</b>	<b>541#</b>		<440#
EPI nmol/24 h	<b>15*</b>	<b>45#</b>	<b>64#</b>		<110#
NMN nmol/24 h		<b>391#</b>	<b>314#</b>		<240#
MN nmol/24 h		<b>97#</b>	<b>90#</b>		<275#
Plasma-free MN					
NMN pg/mL				<b>251**</b>	<149
MN pg/mL				<b>56**</b>	<58

Abnormal results are in bold.

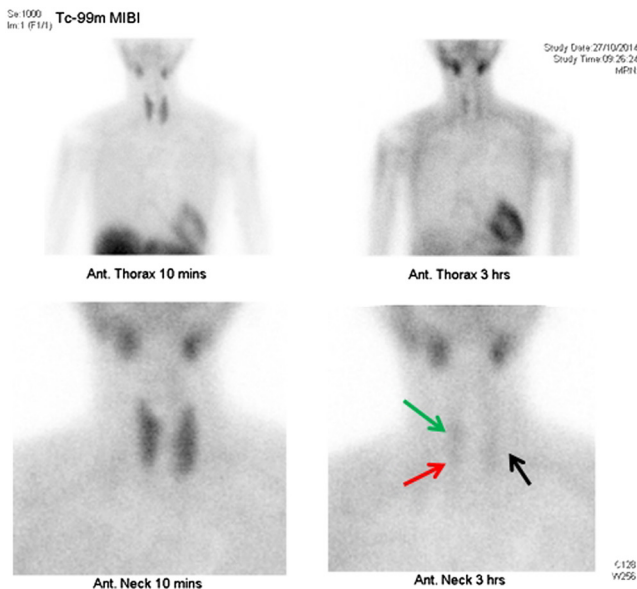
\*Performed in Hospital A using liquid chromatography-tandem mass spectrometry (LC-MS/MS) – reference ranges: NE < 627 nmol/24h, EPI < 86 nmol/24h;

#Performed in Hospital B using liquid chromatography-electrochemical detection (LC-ECD) – reference ranges as listed; \*\*Measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS).

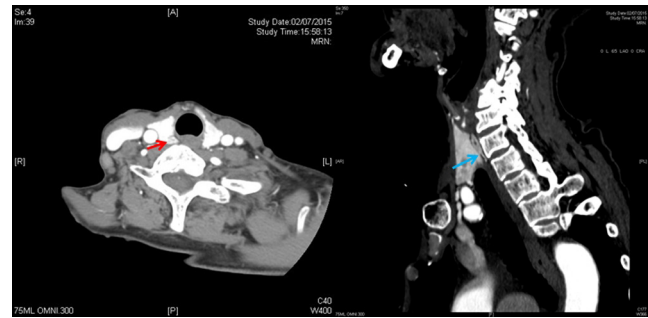
25OHD, 25-hydroxy-vitamin D3; FC, fractionated catecholamines; EPI, epinephrine; NE, norepinephrine; NMN, normetanephrine; MN, metanephrine; PTH, parathyroid hormone.

Meanwhile, she was incidentally found to have mild hypercalcaemia (Table 1), which the clinical focus was then diverted to. Further workup showed an elevated parathyroid hormone (PTH) level of 12 pmol/L (reference range: 1.1–7.3 pmol/L), which was suggestive of PHPT in the presence of hypercalcaemia. A technetium ( $^{99m}\text{Tc}$ )-sestamibi scan showed three very faint foci of delayed washout near the lower pole of left thyroid lobe, the mid-pole of right thyroid lobe and the lower pole of right thyroid lobe (Fig. 2). A neck ultrasonography was suspicious of a 1-cm parathyroid lesion posterior to the right lobe of the thyroid gland. A subsequent 4D-CT confirmed the presence of a parathyroid adenoma (15×4×9 mm) near the mid-pole of right lobe of the thyroid gland (Fig. 3). Minimally invasive right superior parathyroidectomy was performed with intraoperative PTH monitoring in July 2015. A right superior parathyroid adenoma was resected, which was confirmed on surgical pathology. Follow-up biochemical testing revealed normalization of calcium and PTH level.

Our patient returned for scheduled follow-up after the operation and still complained of occasional palpitation. Upon further testing, mildly elevated 24-h urinary norepinephrine (NE) and normetanephrine (NMN) were detected (Table 1), and the suspicion of a PPGL was raised. A CT scan of the adrenals subsequently revealed a 1.9 cm × 1.1 cm (antero-posterior × transverse) hypo-



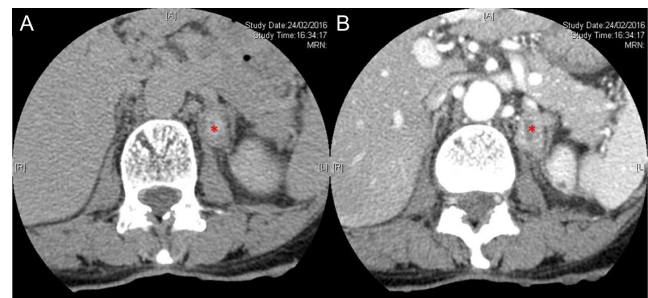
**Figure 2**  
99mTc-Sestamibi scan of the patient. There was faint delayed washout near the lower pole of left thyroid lobe (black arrow), the mid-pole of right thyroid lobe (green arrow) and the lower pole of right thyroid lobe (red arrow).



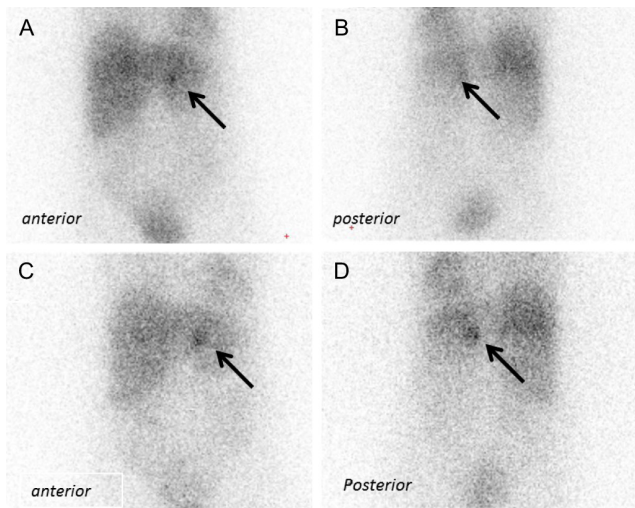
**Figure 3**  
4D-CT of the patient. A 9×4×15 mm hypodense (39 HU) lesion (red arrow) is seen posterior to the upper pole of right lobe of thyroid. It shows early arterial enhancement (210 HU) (A) and shows washout on venous phase (86 HU). Central hypodense centre and polar vessel sign are noted (B) (blue arrow). Enhancement characteristic and imaging features are in keeping with a parathyroid adenoma.

iso-dense lesion over the left adrenal gland. The density of the lesion measured 52 Hounsfield Units (HU) at pre-contrast scan, 103.4 HU at venous phase and 114 HU at delayed phase (Fig. 4) with an absolute washout less than 60%. These imaging features were not compatible with an adrenal adenoma. A  $^{123}\text{I}$ -metaiodobenzylguanidine (MIBG) scintigraphy revealed faint uptake over the left adrenal bed (Fig. 5), which was compatible with a left pheochromocytoma.

Our patient then underwent laparoscopic left adrenalectomy in a tertiary referral centre. Plasma NMN performed preoperatively was elevated as well (Table 1). She was prepared with alpha-blockade using terazocin followed by beta-blockade using propranolol preoperatively. There was mild fluctuation of blood pressure intraoperatively during manipulation of the adrenal tumour with systolic BP up to 190 mmHg, which was aborted with remifentanyl. The intraoperative



**Figure 4**  
(A) Pre-contrast scan: a non-calcified hypo- to isodense lesion (\*) of 1.9×1.1 cm at the region of the left adrenal. Density measured 51.7 HU. (B) Post contrast scan: the density of the lesion measured 103.4 HU at venous phase. The lesion demonstrated delayed enhancement at the central portion, measuring 114 HU. The absolute washout was <60%.



**Figure 5**  
<sup>123</sup>I-MIBG scan of the patient. (A) and (B) At 24 h after <sup>123</sup>I-MIBG injection. (C) and (D) At 48 h post <sup>123</sup>I-MIBG injection. Faint uptake was noted at the left adrenal bed (black arrow).

course was otherwise smooth and the patient ran a smooth recovery postoperatively. The surgical specimen confirmed a pheochromocytoma of the left adrenal gland. Symptoms of palpitation and hypertension resolved after the operation. Follow-up biochemical testing revealed normalization of urinary NE and NMN as well as plasma MNM levels. Disease recurrence was not encountered at the latest follow-up in January 2018. Calcium and PTH levels also remained normal upon 2.5 years of follow-up.

## Discussion

Neurofibromatosis type 1 (NF-1) is a dominantly inherited genetic disorder with a birth incidence of 1 in 2500 to 1 in 3000 (1, 9) and is diagnosed based on established clinical criteria (9, 10). Apart from the frequently found neurofibromas and optic pathway gliomas, patients with NF-1 are at increased risk of various benign and malignant tumours throughout life, including central nervous system tumours, peripheral nerve sheath tumours, gastrointestinal stromal tumours and leukaemia (1, 9). Endocrine diseases and neoplasia also occur in patients with NF-1 which may include PPGLs, PHPT, gastroenteropancreatic neuroendocrine tumour, thyroid and other adrenal tumours (1, 2, 5, 11, 12).

Pheochromocytoma is estimated to have a prevalence of 0.1–14% in NF-1 and may be up to 20–50% in

hypertensive subjects (1, 4, 6, 13). Extra-adrenal paraganglioma (PGL) are uncommon while malignant PPGL may occur up to about 10% of cases (4, 14). A recent large retrospective cohort study by Gruber *et al.* reported the prevalence of pheochromocytoma was 2.9% in 1415 patients with NF-1 by using computer search on patient databases (7). On the other hand, two prospective studies where consecutive patients with NF-1 were screened for pheochromocytoma showed a much higher prevalence of 7.7% (13) and 14.6% (6). Such a large discrepancy is explained by the fact that current guidelines do not recommend routine screening in asymptomatic or normotensive subjects so that reported prevalence rates differed amongst retrospective studies based largely on case finding and prospective studies based on disease screening. Indeed, pheochromocytoma in NF-1 can be entirely asymptomatic and not infrequently present as adrenal incidentaloma. Typical symptoms such as palpitation, headache, hyperhidrosis and paroxysmal hypertension were found in slightly more than half (58%) of the patients by Gruber *et al.* (7) while Képénékian *et al.* reported their presence in 33% (4 out of 12 patients) only (13). On the other hand, 31, 56 and 100% of patients were reported to present as adrenal incidentaloma by Gruber *et al.* (7), Shinall *et al.* (15) and Mormarco *et al.* (16) respectively. Nevertheless, the presence of symptoms and/or hypertension and/or an adrenal incidentaloma should alert the clinician to test for the presence of a PPGL in all subjects with NF-1.

The characteristics of PPGLs in NF-1 also varied amongst different studies. While Shinall *et al.* reported in their cohort of 56 patients with pheochromocytoma that patients with NF-1 had smaller pheochromocytoma and less hypertension compared with those with sporadic pheochromocytoma (15), the American-European Pheochromocytoma Study Group (14) and Mormarco *et al.* (16), which included 565 and 145 patients with pheochromocytoma respectively, found that the clinical characteristics of pheochromocytoma in NF-1 were indistinguishable from those of their sporadic counterparts. They also found that patients with NF-1 presented at an older age (mean age 45 years) when compared with other genetically predisposed syndromes (mean age 30 years) (14, 16). In addition, the secretory behaviour of pheochromocytoma in NF-1 may be more variable as previously thought. While Eisenhofer *et al.* suggested that pheochromocytoma in NF-1 mainly secreted epinephrine (EPI)/metanephrine (MN) (17), Gruber *et al.*, Képénékian *et al.* and Mormarco *et al.* observed that





pheochromocytoma in NF-1 could be predominantly or purely NE/NMN secreting and sometimes non-secretory (MN/NMN less than two times upper limit of normal) (7, 13, 16). The levels of metanephrines may not correlate well with symptoms though higher levels of metanephrines were generally observed in patients with larger tumours (7, 13). Scintigraphy effectively picked up pheochromocytoma in NF-1 with a sensitivity of around 90% for MIBG scan and almost 100% for F-DOPA-PET-CT (13, 16). Therefore, even very modest elevation of metanephrines in any NF-1 patient should be carefully evaluated for the presence of a PPGL, as small tumours may only produce minute excess of metanephrines as exemplified by our patient. In addition, it is recommended to obtain measurement of metanephrines (plasma or urinary) rather than catecholamines as initial biochemical testing of PPGLs due to their superior sensitivities as illustrated in the present case (18).

Although general consensus on screening of pheochromocytoma in asymptomatic and normotensive NF-1 subjects is lacking, emerging data suggest benefit in routine PPGL screening of all individuals with NF-1. The Mayo Clinic group recommended routine case detection testing for all patients with NF1 with plasma-free metanephrines or 24-h urine fractionated metanephrines and catecholamines every 3 years starting from age 10–14 years (7). This is based on the observation that not all patients would present with symptoms, while the three-yearly schedule is considered sufficient compared to the yearly schedule in other familial paraganglioma syndromes of which the prevalence of pheochromocytoma is higher. The cost-effectiveness of such a strategy remains to be tested.

By contrast, the association between PHPT and NF-1 is less clear. Since 1970s, there have been approximately 20 cases of PHPT in NF-1 reported in the literature (5, 8, 19, 20, 21, 22). The mean age of presentation was around 45 years while osteoporosis was a common feature. The majority of patients harboured a solitary parathyroid adenoma or single gland hyperplasia (8, 19). In the only population-based cancer registry study where data on parathyroid pathology was available, only 1 out of 71 NF-1 patients had parathyroid adenoma (5). Therefore, given the lack of epidemiological or functional studies, the link between PHPT and NF-1 remains unsubstantiated. Nevertheless, high prevalence of skeletal diseases and metabolic bone defect has been reported in subjects with NF-1 (1, 23, 24). The presence of PHPT may further exacerbate the bone diseases in these patients and when

it is recognised, treatment should be considered based on the current guidelines (25).

Intriguingly, the concurrence of pheochromocytoma and PHPT has also been reported in a few cases (21, 22, 26, 27, 28). Behera *et al.* reported a 33-year-old gentleman with NF-1 harbouring both a right pheochromocytoma and a left inferior parathyroid adenoma (21). AL-Wahhabi *et al.* (22) and Altinova *et al.* (26) reported two similar patients with NF-1 having bilateral pheochromocytoma and a parathyroid adenoma. Gkaliagkousi *et al.* (27) and Cotesta *et al.* (28) both reported the presence of pheochromocytoma, parathyroid adenoma and medullary thyroid carcinoma in patients with NF-1 confirmed by genetic testing, mimicking full-blown picture of MEN-2A. Patients with overlapping features of NF-1 and MEN-2 harbouring both germline mutations on *NF1* and *RET* have also been reported (29, 30). Indeed, Diazi *et al.* have reported thyroid C-cell hyperplasia and abnormal calcitonin response to pentagastric stimulation in 7 out of 17 patients with NF-1, suggesting a link of NF-1 to thyroid C-cell pathology (31). It has been suggested that NF-1 in association with PHPT and PPGL may be a variant of MEN-2 (20). Despite the above observations, more systemic studies are required to establish whether there exists true relationship between NF-1 and MEN-2.

In conclusion, we herein reported the rare co-occurrence of pheochromocytoma and parathyroid adenoma in a patient with NF-1. This widens the spectrum of endocrine diseases that may be encountered in the management of subjects with NF-1. All NF-1 patients with hypertension or symptoms suggestive of PPGL should undergo biochemical testing by plasma free or urinary fractionated metanephrines and any elevated values should be carefully followed and investigated. The association between PHPT and NF-1, and that between NF-1 and MEN-2, remains at best plausible and need to be further elucidated with systemic and functional studies.

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#### Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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### Patient consent

Written informed consent has been obtained from the patient for the publication of the submitted article and accompanying images.

### Author contribution statement

Both Dr Tam V H K and Dr Fok C K have made significant contribution to the overall management of the patient and the proof-reading of the manuscript.

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