

An elusive pheochromocytoma

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Clinical record

A 56-year-old woman, with a history of a right adrenal pheochromocytoma excised in 1974, presented to the emergency department in 2008 with a hypertensive crisis characterised by 3 days of severe headache, malignant hypertension (blood pressure, 200/115 mmHg) and seizures complicated by bilateral humeral fractures. After her surgery in 1974, she had unresolved hypertension and raised urinary catecholamine levels suggestive of residual or metastatic disease. However, no additional tumour could be identified despite venous sampling studies. The patient declined further treatment and was lost to follow-up from 1978. She subsequently had three uncomplicated, successful pregnancies.

During the patient's 2008 hospital admission, her levels of urinary catecholamines and plasma metanephrines were elevated (Box 1). She was treated with phenoxybenzamine and diltiazem (extended release), doses of which were titrated up to 60 mg twice daily and 360 mg daily, respectively, before uneventful surgical repair of both humeral fractures. Localisation studies with a 123 I-metaiodobenzylguanidine scan identified increased tracer uptake within both the left adrenal region and left anterior mediastinum. Computed tomography and magnetic resonance imaging (MRI) scans showed large bilateral renal angiomyolipomas (AMLs), a right renal artery aneurysm, a bulky left adrenal gland with no discrete mass lesion, and a 15 mm calcified lesion within the left anterior mediastinum (not related to the sympathetic chain). Results of a positron emission tomography scan were negative. However, an octreotide scan showed mild tracer uptake in the left adrenal region and marked focal uptake within the left anterior mediastinum (Box 2).

It was felt unlikely that the left adrenal gland image represented a pheochromocytoma and likely that the mediastinal lesion was a phaeo-chromocytoma lymph node metastasis. After the addition of atenolol 100 mg daily to the patient's drug regimen, the left anterior mediastinal lesion was excised via a cervical approach without complication. Histological examination confirmed a pheochromocytoma metastasis within a lymph node. After the operation, blood pressure improved significantly. Plasma metanephrine levels have remained normal for over a year.

Tests for pheochromocytoma genetic syndromes revealed a missense mutation (Gly144Arg) on exon 2 of the von Hippel-Lindau (VHL) gene, and we are awaiting testing of the patient's eight siblings to determine whether or not this is a de novo mutation causing VHL disease. Although two of her three children have inherited the mutation, they have had no disease manifestations. Further investigations of the patient have revealed mild sensorineural hearing loss, but no evidence of haemangioblastomas via fundoscopy or on MRI scanning of the brain and spinal cord. While there is an increased risk of renal cell carcinoma with VHL disease, recent imaging has shown no change in the patient's presumed bilateral AMLs and she has declined surgery or embolisation. The left adrenal gland and right renal artery aneurysm have also remained stable on serial imaging. Malignant pheochromocytoma has been reported to be a risk factor for osteoporosis,¹ but the patient's bone mineral densitometry showed only osteopaenia of her lumbar spine, while her left hip bone measurements were within normal limits. ♦

Our patient's history shows the need for long-term periodic follow-up of people treated for pheochromocytomas. It also illustrates the association between von Hippel-Lindau (VHL) disease and pheochromocytoma. VHL disease, an autosomal dominant condition, is caused by a mutation of the VHL tumour suppressor gene on chromosome 3p; the mutation rate is one in 36 000 live births.² The VHL gene is involved in regulating the transcription of vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF) and other hypoxia-inducible proteins. Inactivation promotes tumour angiogenesis and growth through overexpression of VEGF and PDGF receptor agonists, resulting in haemangioblastomas of the central nervous system or retina, pancreatic neuroendocrine tumours and cysts,

renal clear cell carcinomas, pheochromocytoma, endolymphatic sac tumours, and papillary cystadenomas of the epididymis (men) or broad ligament (women).³

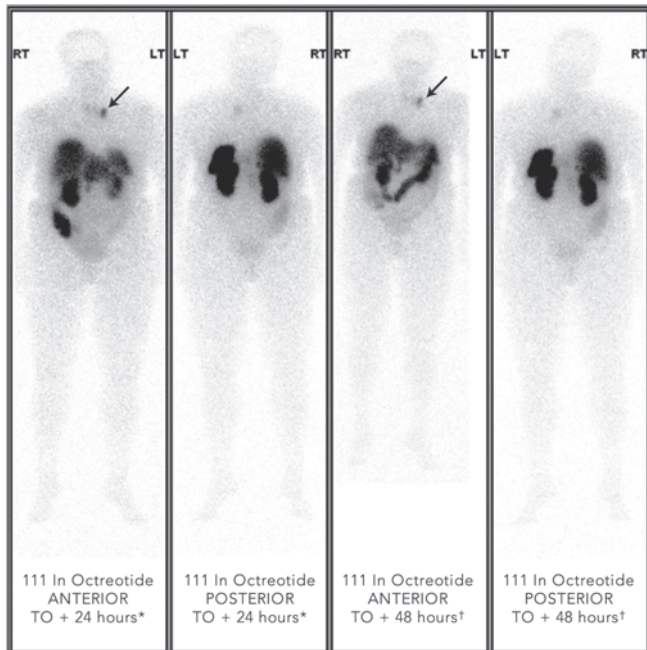
In a series report of 246 patients with VHL disease, 26% of patients developed pheochromocytomas at a mean age of 29 years, 39% had bilateral adrenal pheochromocytomas, and extra-adrenal disease occurred in up to 30%.⁴ The adrenal medulla is the main site in the body where the enzyme that converts noradrenaline to adrenaline, phenylethanolamine N-methyltransferase, is localised, and, consequently, adrenal pheochromocytomas typically have raised levels of both noradrenaline and adrenaline. By contrast, extra-adrenal pheochromocytomas and pheochromocytomas in patients with VHL disease do not usually express

1 Patient's levels of urinary catecholamines and plasma metanephrines at pheochromocytoma diagnosis and post-treatment, and metastasis diagnosis and post-treatment

Investigation	1974	Surgery 1974	1976	Investigation	2008	Surgery September 2008	April 2009	Feb 2010
Urine noradrenaline (RR, < 80 µg/d)	1681.8*		851.4*	Urine noradrenaline / Cr (RR, 0–60 nmol/mmol)	152.3		58.2	48.5
Urine adrenaline (RR, < 20 µg/d)	86.5*	4.7*	Urine adrenaline / Cr (RR, 0–10 nmol/mmol)	17	< 1.3	< 2.5		
Plasma normetadrenaline	Assay not available	Assay not available	Plasma normetadrenaline (RR, < 900 pmol/L)	3680	658	692		
Plasma metadrenaline	Assay not available	Assay not available	Plasma metadrenaline (RR, < 500 pmol/L)	591	113	122		

Cr = creatinine. RR = reference range. * Noradrenaline and adrenaline / Cr ratios unavailable. ♦

2 Octreotide scans of patient with pheochromocytoma metastasis showing abnormal focal tracer uptake in anterior mediastinum (arrows in anterior views)



* Scan 24 hours after intravenous injection of radioactive octreotide.
 † Scan 48 hours after intravenous injection of radioactive octreotide.

Lessons from practice

- Persistent hypertension and elevated catecholamine levels after excision of a pheochromocytoma are suggestive of residual or metastatic disease.
- Patients with a history of pheochromocytoma require long-term surveillance.
- Between 12% and 24% of patients with ostensibly sporadic pheochromocytomas harbour predisposing genetic syndromes, including von Hippel–Lindau (VHL) disease, and genetic screening is recommended in patients diagnosed under 50 years of age.
- VHL disease is a dominantly inherited syndrome, involving mutation of the *VHL* tumour suppressor gene — the mutation occurs in one in 36 000 live births.

input. In the case of VHL disease, biochemical screening for pheochromocytomas should start at age 4 years, and tumours should be removed if functional, as indicated by elevated catecholamine levels.⁴ While our patient's experience highlights the importance of screening for underlying germline mutations, it also reinforces the unpredictable nature of pheochromocytoma metastases.

Competing interests

None identified.

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(Received 20 May 2010, accepted 21 Oct 2010)

phenylethanolamine N-methyltransferase and are therefore characterised by raised levels of noradrenaline and normetadrenaline with relatively normal levels of adrenaline and metadrenaline. For our patient, elevations in noradrenaline levels exceeded those of adrenaline both at the time of the original pheochromocytoma diagnosis and subsequently, with adrenaline levels normalising after the original operation, in keeping with extra-adrenal or metastatic disease. Kindreds with VHL disease can be divided into two types (Types I and II) based upon the incidence of pheochromocytoma, with Type I generally unaffected and Type II at high risk.⁵ Type II is further divided — IIA and IIB have a low or high incidence of renal clear cell carcinomas, respectively, while IIC is characterised by the development of pheochromocytomas without other VHL manifestations. Of the 1548 reported mutations in the *VHL* gene, 52% are missense mutations and the one previously reported Gly144Arg mutation was associated with polycythaemia.⁶

Renal angiomyolipomas (AMLs) occur in 0.1% of the population, and although those with bilateral renal AMLs have a greater chance of having tuberous sclerosis, this patient has no other features of the condition.^{7,8} However, it is possible that she has a new phenotype of Type II VHL disease associated with AMLs.

Between 12% and 24% of patients with ostensibly sporadic pheochromocytomas harbour pheochromocytoma genetic syndromes, including VHL disease. A study of 271 such patients detected a germline *VHL* mutation in 11%, increasing to 42% in those who presented at age 18 years or younger.⁹ Therefore, it is recommended that patients diagnosed with a pheochromocytoma before the age of 50 years should undergo screening for underlying germline mutations.¹⁰ For relatives identified as having predisposing germline mutations, investigations and follow-up are dictated by the underlying disease, but should include clinical genetics and endocrinological