CASE REPORT

Giant phaeochromocytoma presenting with an acute stroke: reappraising phaeochromocytoma surveillance for the neurofibromatosis type 1 phakomatosis

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Accepted 13 October 2017

SUMMARY

Neurofibromatosis type 1 (NF1) is a multisystem genetic disorder associated with reduced lifespan attributed largely to malignancy and vascular causes. One of the tumours associated with NF1 is phaeochromocytoma. The phaeochromocytoma has earned the moniker, a 'great mimicker', due to its varied means of presentation. We present a patient with NF1 who was diagnosed with a giant 20 cm phaeochromocytoma after suffering from an ischaemic stroke. Current guidelines do not advocate surveillance of phaeochromocytoma in asymptomatic patients with NF1, unlike other genetic syndromes associated with phaeochromocytoma. However, there is increasing evidence that this approach may not help in the early detection and treatment of this potentially life-threatening disease. Our patient remained hypertensive after surgery despite achieving biochemical cure. The suggested chronicity of the underlying tumour in our patient is a reminder to practising clinicians to rethink our strategy in identifying phaeochromocytoma in adults with NF1.

BACKGROUND

Phaeochromocytoma is known as a great mimicker of diseases. Although largely a sporadic tumour, underlying genetic mutations have been identified in up to one-third of non-syndromic patients. Genetic syndromes, such as multiple endocrine neoplasia type 2, von-Hippel Lindau disease (vHL) and type 1 neurofibromatosis (NF1) harbour genetic mutations with a predilection for this tumour. In patients with these syndromes, the crux lies in detecting the tumour in its infancy to maximise the chance of cure and reduce complications. In our case presentation, the patient with NF1 did not receive any routine surveillance for the tumour and presented only when she suffered an ischaemic stroke. We would like to bring attention to the increased morbidity of untreated phaeochromocytoma, and to highlight the importance of considering this tumour in appropriate settings when encountering patients with NF1.

CASE PRESENTATION

A 49-year-old Chinese woman with NF1 was admitted complaining of a 3-day history of right-sided weakness. She was previously well and did not attend any regular medical check-ups with her primary healthcare provider. She did not consume alcohol and was a non-smoker. Four out of nine of her siblings suffered from NF1, but none suffered from cardiovascular disease.

On physical examination, the patient was alert and vital signs revealed a blood pressure (BP) of 165/70 mm Hg and a pulse rate of 100 beats per min. Neurological examination confirmed right hemiparesis. Peripheral pulses were bilaterally equal. There were no carotid bruits and cardiorespiratory examination was unremarkable. Significantly, a large and firm ballotable mass measuring 15 cm over the left flank of the abdomen was found.

INVESTIGATIONS

Routine blood investigations showed normal full blood count and renal function. Low-density lipoprotein (LDL) was elevated at 4.6 mmol/L. Fasting blood glucose was normal. Evaluation for other causes of young hypertension and young stroke were negative (table 1).

An acute ischaemic stroke was confirmed on MRI of the brain, which showed an infarct in the left internal capsule contributed by a stenosis in the M1 segment of the left middle cerebral artery.

To evaluate for the abdominal mass, a CT of the abdomen was performed and revealed a heterogeneous 18 cm left adrenal mass with cystic areas of necrosis (figure 1A,B). The right adrenal was normal.

DIFFERENTIAL DIAGNOSIS

While an acute ischaemic stroke in a patient with NF1 could be attributed to underlying atherosclerotic processes, some differential diagnoses deserve attention. Conditions such as Moya Moya disease (with associated renovascular hypertension) and adrenal pathologies such as phaeochromocytoma and primary hyperaldosteronism can contribute to both hypertension and strokes.

Further history revealed that the patient had spells of palpitations and diaphoresis lasting about 1 min each in the past few months, but had dismissed them as anxiety attacks. As this patient has underlying NF1 and a ballotable left flank mass, the diagnosis of phaeochromocytoma must be seriously considered given this suggestive history. Taken together with the CT images, this must be the diagnosis until proven otherwise.

Hormonal assessment for adrenal hypersecretion was performed. The only abnormality

To cite: Lee Y, Tan LYR, Ho YH, *et al*. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-222553

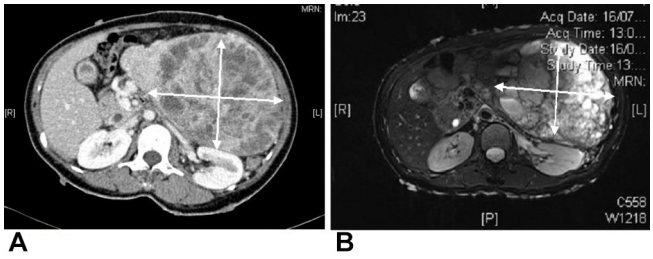

Figure 1 (A) CT abdomen showing a large 18 cm x 20 cm heterogeneous mass with areas of necrosis and mass effect on adjacent structures. (B) MRI abdomen of the same intra-abdominal mass showing hyperintensity on T2.

was marked elevation of the 24 hours urinary catecholamines and metanephrines at 111 500 nmol/day (reference intervals 480–2424 nmol/day) and 54 619 nmol/day (reference intervals 264–1729 nmol/day), respectively. Aldosterone and renin levels did not fulfil the required criteria for either primary or secondary hyperaldosteronism.

The diagnosis of phaeochromocytoma was, therefore, confirmed biochemically.

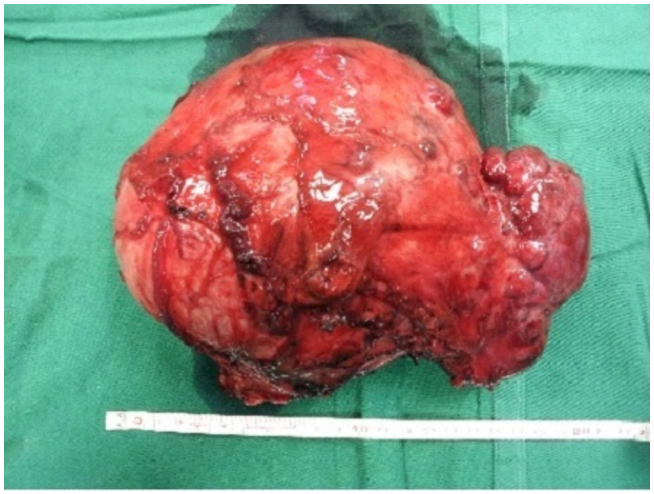

Figure 2 A large 20 cm phaeochromocytoma removed en bloc during surgery.

TREATMENT

The patient was seen in consultation with an endocrine surgeon and counselled for a left adrenalectomy. She received

Table 1 Investigations for young stroke were performed and were all normal

	Results	Units	Reference intervals
Haematology			
Haemoglobin	13.5	g/dL	11–15
Haematocrit	41.0	%	35–45
Total white cell count	8.4	x 10^9/L	3.6–9.3
Platelet count	405	x 10^9/L	170–420
Electrolytes			
Sodium	138	mmol/L	134–144
Potassium	4.3	mmol/L	3.5–5.0
Creatinine	69	µmol/L	40–75
Calcium, adjusted	2.25	mmol/L	2.15–2.58
Atherosclerosis risk factors			
Glucose, fasting	5.5	mmol/L	3.0–6.0
HbA1c	5.7	% mmol/L	54.5–6.4
Total cholesterol	6.7	mmol/L	<6.2
High-density lipoprotein	1.5	mmol/L	>1.0
Low-density lipoprotein	4.6	mmol/L	<4.1
Triglycerides	1.4	µmol/L	<2.3
Homocysteine, S	8		5–15
Coagulability profile			
PT	11.8	s	11.7–14.0
PTT	27.6	s	25.0–36.0
Lupus anticoagulant	Absent	–	–
Vasculitis screen			
Anti-dsDNA	Negative	IU/mL	<25
Anticardiolipin IgM	1	MPL U/mL	<10
Anticardiolipin IgG	2	GPL/mL	<10
ECG	Normal sinus rhythm		
2D echocardiography	Ejection fraction >55%, no valvular abnormalities, no thrombus, no intracardiac shunt		–
Inpatient 48 hours Holter monitoring	Negative for atrial fibrillation		–
Ultrasound of carotid arteries	Bilateral internal carotid arteries <40% stenosis Common carotid arteries, external carotid arteries and vertebral arteries normal		–
Transcranial Doppler with bubble study	Negative for cardiac right-to-left shunt		–

2D, two dimensional; dsDNA, double-stranded DNA; PT, thrombin time; PTT, partial thromboplastin time, MPL- IgM Phospholipid GPL- IgG Phospholipid.

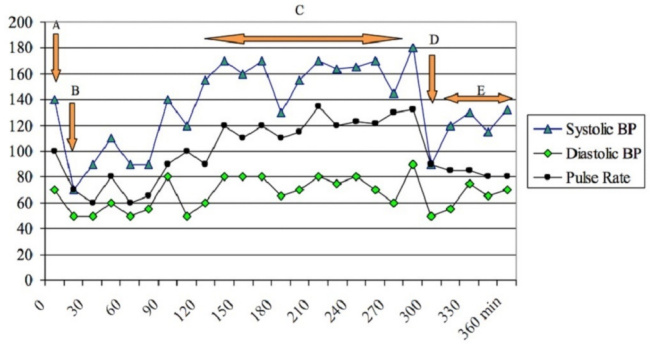

Figure 3 Blood pressure (BP) and pulse rate trends during operation. (A) At induction; (B) after intubation (intravenous phenylephrine given); (C) surgical manipulation of tumour (intravenous $MgSO_4$ given); (D) surgical resection of tumour; (E) recovery.

preoperative preparation with oral phenoxybenzamine 10 mg two times per day, followed by atenolol 25 mg subsequently for reflex tachycardia. After adequate adrenergic blockade and intravascular volume expansion, she underwent an elective open-left adrenalectomy where a giant 20 cm x 14 cm x 10 cm phaeochromocytoma was removed en bloc (figure 2). Despite adequate preoperative preparation, she still experienced intraoperative fluctuations in BP between systolic 70 and 170 mm Hg (figure 3).

It was histologically confirmed to be a composite phaeochromocytoma with ganglioneuroma elements (figure 4A,B).

Postoperatively, the urinary catecholamines and metanephrines were normalised (table 2). One month later, hypertension was recurred. Both biochemical and radiological tests were negative for recurrence. A 131-iodine-metaiodobenzylguanidine scintigraphy scan did not detect any tracer avid lesion. Screen for other secondary causes of hypertension was negative. She was started on nifedipine LA 30 mg daily and prazosin 1 mg two times per day and achieved good BP control.

OUTCOME AND FOLLOW-UP

Currently, it is 4 years postsurgery, and she remains well without any suggestive symptoms of recurrence. At home, her BP is well controlled, and her urinary catecholamines and metanephrines had remained normal during regular 6 monthly check-ups.

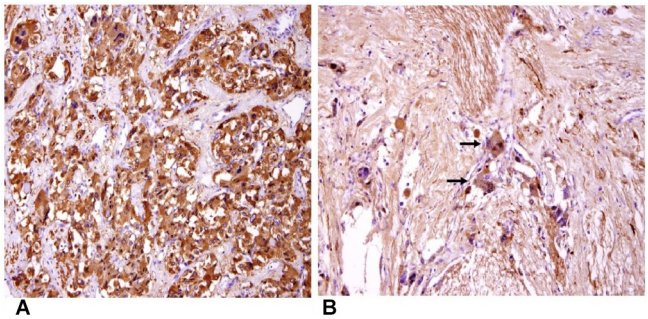

Figure 4 (A) Immunohistochemical staining for synaptophysin highlights the neoplastic cells in the phaeochromocytoma component of the tumour (original magnification ×200). (B) The neurofibrillary matrix and the scattered ganglion cells (arrows) in the ganglioneuroma component are highlighted by immunohistochemical staining for S100 protein (original magnification ×200).

DISCUSSION

The association between NF1 and phaeochromocytoma is well established. Its incidence in NF1 is 0.1%–5.7%, roughly 10 times that of the general population.[1-6]Among hypertensive NF1 patients, the tumour is present between 20% and 56%. Phaeochromocytoma in NF1 is unilateral and intra-adrenal in more than 80%, and has a malignant rate of about 10%.[7–11] Available guidelines suggest screening for the condition with urinary or serum metanephrines only when typical symptoms are present.[12–14]

The most common symptoms of phaeochromocytoma are hypertension, headaches, palpitations and diaphoresis.[10 15] Hypertension is common in NF1. It increases with age and occurs between 2% and 15.8%.[16 17] Secondary causes of hypertension are associated with NF1, including renal artery stenosis, coarctation of aorta and phaeochromocytoma. In a preadolescent child, the most common secondary cause is renovascular disease and this must be sought thoroughly as secondary hypertension can be found in up to 85%.[18 19] In an adult, phaeochromocytoma becomes more common although no cause is found in the majority. The likelihood of an underlying secondary cause becomes higher in the event of refractory high BP or when hypertension occurs in pregnancy.

Phaeochromocytoma has been given the moniker ‘a great mimicker’ and can present with symptoms from almost any other system. Asymptomatic disease has also been reported and the incidence ranges between 11% and 48% in retrospective studies.[20–22] In NF1 populations, recent retrospective studies agreed with the above findings, where symptoms of catecholamine excess were absent in 22%–42%, and hypertension was absent in 23%–83%.[8 9 11] It is important to note that 31%–100% of phaeochromocytomas were diagnosed incidentally in these studies. Among the genetic syndromes associated with phaeochromocytoma, NF1 remains the only one where routine surveillance for the condition is currently not practised.[23–25] Based on the above evidence, the approach of screening only hypertensive or symptomatic patients with NF1 may result in missed or delayed diagnosis in NF1.

Zinnamosca *et al* and Kepenekian *et al* evaluated a different approach to the detection of phaeochromocytoma in NF1.[26 27] In both studies, asymptomatic NF1 patients were recruited for screening. Zinnamosca *et al* assessed 48 consecutive NF1 patients using urinary metanephrines and vanillylmandelic acid excretion while Kepenekian *et al* screened 156 consecutive NF1 patients with a combination of abdominal imaging (ultrasound or CT) and urinary fractionated metanephrines. This was followed by a functional scan with either ^{123}I-metaiodobenzylguanidine scintigraphy or 18F-fluoro-dihydroxyphenylalanine if the screen was positive. The prevalences of phaeochromocytoma in the two studies were 14.6% and 7.7%, respectively.[26 27] More than half of the subjects in both studies were asymptomatic. The smallest tumour was 1 cm while the largest was 5 cm. Interestingly, half of the cases in the Kepenekian study were non-secretory with tumour sizes smaller than the secretory tumours (mean 1.40 vs 2.52 cm).

In this case study, stroke was the initial presentation that led to the discovery of a giant 20 cm phaeochromocytoma and hypertension. The patient was not diagnosed with hypertension prior to this. Both NF1 and phaeochromocytoma have been associated with increased risk of cerebrovascular disease.[28–30] In addition to hypertension, underlying NF1 vasculopathy may be a contributing factor. NF1 vasculopathy is a less discussed but well described complication. It involves

Table 2 Urinary catecholamines and metanephrines trend from preoperative to postoperative, showing normalisation of results after surgery

	Preoperative	Months postoperative						Reference intervals
		1	6	11	17	20	30	38	
U Catecholamines									
Total urine volume	1800	900	1500	1400	1600	2000	1800	1773	mL
Epinephrine, 24 hours	265	20.2	<10	<10	<10	<10	94	21	9.3–122.0 nmol/day
Norepinephrine, 24 hours	920	317	113	157	165	128	169	170	72–505 nmol/day
U Metanephrines									
Total urine volume	1800	900	1500	1400	1600	2000	1800	1773	mL
Metanephrines, 24 hours	64 692	548	174	227	217	186	279	213	264–1729 nmol/day
Normetanephrine, 24 hours	1 25 200	3370	737	1289	1538	836	1145	1073	480–2424 nmol/day

a spectrum of vascular disorders affecting both peripheral and cerebral vessels, with Moya Moya syndrome being the pathognomonic description. The abnormalities seen in NF1 vasculopathy can range from stenosis, aneurysms to arterio-vascular malformations. The underlying pathophysiology is related to disorganised endothelial repair associated with a defective *NF1* gene.[31–33] The risk of an ischaemic stroke in catecholamine-producing tumours may be attributed to a few factors—uncontrolled hypertension, vascular spasm, dilated cardiomyopathy with a risk of left ventricular thrombus and labile BP with hypotensive episodes causing increased susceptibility in watershed regions. There is also evidence that catecholamines are involved in vessel remodelling and associated with increased intima media thickness of carotids.[34 35]

Given the size of the tumour, it is likely that she had been harbouring it for much longer than the duration of her reported symptoms. It is unfortunate that she was diagnosed only after presenting with a complication related to both phaeochromocytoma and hypertension. As she is not cured of hypertension even after surgery, her cardiovascular risks remain appreciable.

The current approach to phaeochromocytoma screening in NF1 is fraught with shortcomings and pitfalls. Delayed or missed diagnoses of phaeochromocytoma would contribute to increased morbidity and mortality of this dangerous condition.

Screening for phaeochromocytoma only when patients with NF1 develop hypertension or typical symptoms is likely inadequate. This traditional method exposes the patient to the deleterious effects of catecholamine excess as seen in this case. We await more studies to recommend a cost-effective method of phaeochromocytoma screening in NF1 populations. Meanwhile, physicians should be cognisant of this rare but dangerous tumour associated with NF1, and have a low threshold for screening until clearer guidelines are available.

Learning points

- Delayed or missed diagnosis of phaeochromocytoma contributes to increased morbidity and mortality.
- NF1 is associated with both essential and secondary hypertension. Regular surveillance for hypertension in this group of patients is important as vascular causes contribute to an increased mortality in NF1 patients.
- When diagnosed with hypertension, tests to exclude secondary causes, including phaeochromocytoma must be performed in NF1 patients.
- Physicians should be aware of the association of this rare and dangerous tumour with NF1 and have a low threshold for screening while awaiting further guidelines.

Contributors YL conceived the idea for the manuscript, analysed the data and wrote the majority of the manuscript. LYRT assisted in literature research and writing of the case. YHH provided critical review of the manuscript as well as assisting in the elucidation of the pathological diagnosis of the case. MKSL provided invaluable guidance in intellectual input, critical review and editing of the manuscript for scientific content validity and accuracy.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

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