Dopamine-secreting phaeochromocytomas and paragangliomas: clinical features and management

Foo S H, Chan S P, Ananda V, Rajasingam V

ABSTRACT

Most functional phaeochromocytomas/paragangliomas produce noradrenaline and/or adrenaline. Those that produce dopamine are rare. We describe the distinguishing clinical features of dopamine-secreting phaeochromocytomas and paragangliomas from those that secrete noradrenaline/adrenaline and the impact on their management. We present a case of a dopamine-secreting paraganglioma from our institution and review 14 case reports of dopamine-secreting phaeochromocytomas/paragangliomas published between 1984 and 2008. As observed in the literature, 80% of the tumours were extra-adrenal. Most patients presented with non-specific symptoms or mass effect without the classical presentation of catecholamine excess. The majority were diagnosed with urinary or plasma dopamine. Five patients had malignant tumours and 12 patients underwent surgical resection of the primary tumours. Unlike noradrenaline/adrenaline-secreting phaeochromocytomas/paragangliomas, dopamine-secreting tumours lack a classical presentation, are extra-adrenal and have a higher malignant potential. A routine inclusion of urinary or plasma dopamine as part of catecholamine screening in all suspected phaeochromocytomas and paragangliomas is recommended.

Keywords: dopamine-secreting tumours, functional paraganglioma, phaeochromocytoma, plasma dopamine, urinary dopamine

Singapore Med J 2010;51(5):e89-e93

INTRODUCTION

Phaeochromocytomas are neuroendocrine tumours that originate from chromaffin cells within the adrenal medulla or sympathetic paraganglia that produce, metabolise and secrete excess catecholamines. About 10% of the tumours are extra-adrenal, and these are referred to as paragangliomas. Paragangliomas, where the autonomic paraganglia are located, can be divided into four groups: brachiometric, intravagal, aorticosympathethic and visceroautonomic. Most functional phaeochromocytomas/paragangliomas produce noradrenaline (NAd) and/or adrenaline (Ad). Tumours that produce predominantly or exclusively dopamine (DA) are rare. The purpose of this report is to highlight the distinguishing features of DA-secreting phaeochromocytomas/paragangliomas and to determine how their management may differ from that of those that secrete NAd/Ad. We present a case of DA-secreting paraganglioma from our institution and review 14 case reports of DA-secreting phaeochromocytomas/paragangliomas published between 1984 and 2008, with regard to their clinical presentation and management.

Table I. Results of urinary catecholamine studies (urine volume = 2.21 litres).

Urine catecholamine	Result	Reference range
24-hour urine NAd (nmol)	898.8	71.0–505.3
Urinary NAd: creatinine (μmol/mol)	122.4	5.9–41.2
24-hour urine adrenaline (nmol)	132.0	9.2–122.3
Urinary Ad: creatinine (μmol/mol)	18.0	0.8–6.6
24-hour urine dopamine (μmol)	2558.0	0–3.2

NAd: noradrenaline; AD: adrenaline

CASE REPORT

A 64-year-old Chinese woman presented at our institution in July 2006 with weight loss and abdominal swelling. There was no history of hypertension or symptoms suggestive of catecholamine excess. On examination, the patient's blood pressure was 145/80 mmHg with a pulse rate of 95 beats per minute. There was a ballotable mass in the left upper quadrant of the abdomen. Urinary catecholamine studies showed predominant excess DA secretion (Table I). Computed tomography of the abdomen revealed an 11 cm mass in the left para-aortic region with necrosis. DA-secreting para-aortic paraganglioma was diagnosed.

As the urinary NAd and Ad levels were not significantly raised, preoperative α-blockade was not

Endocrine Unit, Department of Medicine, University Malaya Medical Centre, Lembah Pantai, Kuala Lumpur 59100, Malaysia

Foo SH, MBBS, MCRP
Clinical Specialist

Chan SP, MBBS, FRCP
Senior Consultant

Ananda V, MBBS, MRCP
Lecturer

Department of Surgery

Rajasingam V, MBBS, FRCS
Senior Consultant

Correspondence to:
Dr Foo Siew-Hui
Tel: (60) 12369 5454
Fax: (60) 3 7960 5369
Email: jsiewhui@yahoo.com

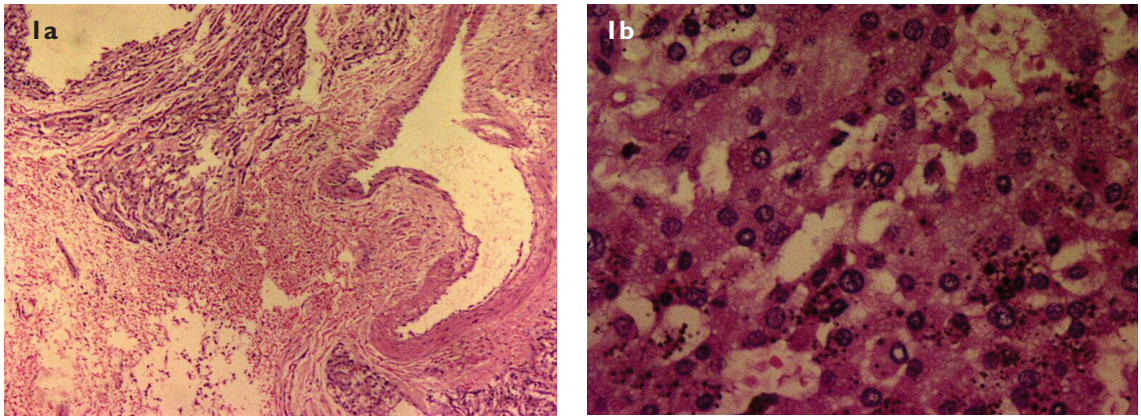

Fig. 1 Photomicrographs show (a) part of the tumour capsule with evidence of capsular invasion at the upper left-hand corner (Haematoxylin & eosin, × 5) and (b) polygonal tumour cells with pleomorphic nuclei, occasional mitotic figures and extensive melanin pigmentation (Haematoxylin & eosin, × 40).

administered. Intraoperatively, a vascular mass measuring 13 cm × 11 cm × 8 cm, which had invaded the surrounding tissue, was found. The blood pressure dropped to 40/20 mmHg from a transient peak of 260/105 mmHg during tumour manipulation. Postoperative recovery was complicated by intractable hypotension requiring inotropic support for five days, although haemostasis was secured within the first 24 hours. The patient's blood pressure remained persistently elevated, which eventually required the prescription of three antihypertensive agents upon discharge. The urinary NAd, Ad and DA levels normalised one month after surgery. Histopathology revealed a circumscribed tumour with capsular invasion (Fig. 1a). The tumour cells were polygonal with abundant eosinophilic cytoplasm and vesicular nuclei. Some nuclei appeared more pleomorphic with occasional mitotic figures (Fig. 1b). A zellballen pattern with focal necrosis was observed. A final diagnosis of malignant paraganglioma with capsular invasion was made.

DISCUSSION

A total of 14 cases of predominantly or exclusively DA-secreting phaeochromocytomas/paragangliomas were reported in the literature between 1984 and 2008.[1-13] The individual patient demographics, clinical features, treatment and outcome are summarised in Table II, including those of our case (Case 1). There were five male and ten female patients, aged 20–71 years (mean 46.3 ± 19.0 years). Out of the 14 cases in the literature, eight (53.3%) were exclusively DA-secreting tumours, while the rest were predominantly DA-secreting tumours that co-secreted NAd and Ad (mixed tumours). Unlike NAd/Ad-secreting tumours, DA-secreting phaeochromocytomas/paragangliomas lack the classical presentation of catecholamine excess (paroxysms of headache, palpitations, diaphoresis and hypertension). The presentations are often non-specific and are usually normotensive. The diagnosis is therefore often delayed until the tumour becomes large enough to cause a mass effect. In the present series, 66.7% of the tumours were at least 10 cm in diameter at diagnosis, with a mean tumour size of 12.0 ± 8.3 cm. There was a much higher incidence (33%–56%) of extra-adrenal tumours among DA-secreting phaeochromocytomas, compared to about 10% reported for NAd/Ad-secreting phaeochromocytomas.[14,15] In the present series, 80% of the tumours were extra-adrenal, with six brachiometric, one intravagal and five aorticosympathethic tumours.

The clinical presentations vary in the present series depending on the tumour location. Intra-abdominal tumours usually present with non-specific abdominal discomfort or backache associated with a palpable abdominal mass. Those in the head and neck regions often present with mass effect, such as neck swelling, hearing disturbance or lower cranial nerve palsies. Only 20% of the patients had symptoms of adrenergic excess, while hypertension was noted in only 13.3% of the patients at presentation. None of the patients presented with a hypertensive crisis. Similarly, in Proye's series of 15 cases of DA-secreting phaeochromocytomas, hypertension was noted in only two cases of mixed tumours, while none of the exclusively DA-secreting tumours was associated with hypertension.[14] DA counteracts, in a dose-dependent fashion, the vasoconstrictor action of NAd via its vasodilatory effect in the renal and mesenteric vascular beds.[9,11,14] At the level of the sympathetic nerve endings, it also inhibits NAd release by acting on the pre-synaptic dopaminergic receptors.[11] Although patients with DA-secreting tumours were often normotensive, perioperative haemodynamic

Table II. Demographics, clinical features, treatment and outcome of 15 patients with DA-secreting phaeochromocytomas/ paragangliomas.

No.	Age	Gender	Clinical presentation	Mode of diagnosis	Imaging findings	Treatment and outcome
1.*	64	F	Weight loss, abdominal mass	Urinary DA	CT: 13 cm left para-aortic mass with local invasion	Surgical resection; urinary DA normalised
2.[1]	20	M	Pulsatile tinnitus, hearing impairment, retrotympanic mass	Tumour DA content (retrospective)	CT: Enhancing left jugular fossa mass extending to cerebellopontine angle and infratemporal fossa	Tumour embolisation and surgical resection; residual tumour present
3.[2]	31	F	Hoarse voice, palpitations, nervousness, diaphoresis, left CN IX-XII palsies	Plasma DA at left jugular vein (selective venous sampling)	CT: 2 cm enhancing left jugular mass	α-blocker given before surgical resection; cardiovascular collapse on postoperative Day 1 and died after six days.
4.[1]	29	M	Hearing loss, left CN VI,VII,IX,X,XII palsies, retrotympanic mass	Tumour DA content (retrospective)	CT: Enhancing left jugular fossa mass eroding into the posterior fossa and inferior cavernous sinus	Tumour embolisation and surgical resection; residual tumour present
5.[3]	40	F	Pulsatile tinnitus	Plasma DA (retrospective)	CT: Left jugular mass de-roofing facial canal and eroding into the jugular foramen	Radiotherapy; developed local recurrence six years later
6.[4]	26	M	Supraclavicular mass, pleural effusion, hepatomegaly	Urinary HVA	CT: 20 cm left retroperitoneal mass with local invasion, deposits in the liver and left hydronephrosis	Died one month after chemotherapy
7.[5]	54	F	Chest pain, dyspnoea	Plasma DA	CT: 3 cm para-aortic mass superior to the left pulmonary artery	Surgical resection; plasma DA normalised and well at one year
8.[6]	65	M	Diarrhoea, weight loss	Urinary DA and HVA, plasma DA	CT: Left adrenal mass and positive ^{131}I-MIBG	Surgically resected; biochemical profiles normalised
9.[7]	76	F	Cervical mass	Urinary and plasma DA	MR: 3 cm carotid body tumour and positive ^{123}I-MIBG	Surgical resection; plasma DA normalised and well at one year
10.[8]	48	M	Cervical mass	Plasma DA	CT / MR: 7 cm × 5 cm × 3 cm left parapharyngeal mass	Tumour embolisation and surgical excision; plasma DA normalised
11.[9]	40	F	Dysphagia, hoarse voice	Plasma DA (retrospective)	CT / MR: Left carotid mass	Surgical resection and radiotherapy; developed extensive metastases (negative ^{131}I-MIBG) and died 11 years later.
12.[10]	26	F	Palpitations, chest pain, headache	Urinary DA	CT: 11 cm × 10 cm × 9 cm right adrenal mass	α-blocker given before surgical resection; urinary DA normalised postoperatively
13.[11]	71	F	Low back pain, weight loss, abdominal mass	Urinary DA	CT: 10.4 cm × 7.3 cm × 5.6 cm right parasagittal mass with hydronephrosis and positive ^{131}I-MIBG	α-blocker given before surgical resection; urinary DA normalised
14.[12]	35	F	Headache, diaphoresis, palpitations	Urinary and Plasma DA	CT: 11 cm left cystic adrenal mass	Preoperative α-blocker stopped before adrenalectomy due to hypotension; biochemical profiles normalised postoperatively and well at seven years
15.[13]	70	F	Right hypochondriac pain, weight loss, anorexia	Urinary DA	CT: 16.2 cm × 11.1 cm × 28.7 cm right retroperitoneal mass	Treated palliatively; died within a few weeks

* Present case

M: male; F: female; DA: dopamine; CT: computed tomography; CN: cranial nerve; HVA: homovanillinic acid; MIBG: meta-iodobenzylguanidine; MR: magnetic resonance

Table III. Summary of differences between DA-secreting vs. NAd/Ad-secreting phaeochromocytomas/paragangliomas.

Tumour type	NAd/Ad-secreting	DA-secreting
Clinical presentation	Symptoms and signs of adrenergic excess	Non-specific or mass effects
Blood pressure		
Preoperative	Elevated	Normal
Postoperative	Low	Elevated
Tumour location	Adrenal	Extra-adrenal
MIBG positivity	86%–90%	60%–67%
Recurrence rate	Lower	Higher
Malignant potential	Lower	Higher
Preoperative α-blockade	Indicated	Not indicated

NAd: noradrenaline; Ad: adrenaline; DA: dopamine; MIBG: meta-iodobenzylguanidine

instability is not uncommon. 60% of the patients in the present series developed perioperative haemodynamic disturbance. Four patients had protracted hypotension postoperatively, while the persistent elevation of blood pressure after tumour resection was documented in four patients, including our case.[11,12] This is believed to be due to rebound hypertension, with an unopposed release of NAd from postganglionic sympathethic neurons following the removal of the source of excess DA.[11,12]

NAd/Ad-secreting phaeochromocytomas are commonly diagnosed by elevated levels of urinary NAd/Ad or its metabolites. The diagnosis of DA-secreting phaeochromocytomas is often missed if urinary or plasma DA is not included as part of the catecholamine screening. Urinary and plasma DA are the most widely used methods in the diagnosis of DA-secreting tumours. However, their sensitivity and specificity in detection remain unknown. Plasma methoxytyramine, the O-methylated metabolite of DA, has been shown to be more sensitive and specific than urinary DA in detecting DA-secreting tumours, as urinary DA is dependent on renal extraction and the decarboxylation of circulating dihydroxyphenylalanine (DOPA) to DA.[16] However, the availability of this assay is limited, and further studies are required to assess its ability to replace urinary or plasma DA. 80% of the patients in the present series were diagnosed with an elevated urinary and/or plasma DA. The diagnosis was missed in three cases at the initial presentation, as urinary DA was not included as part of the preoperative urinary catecholamine screening.[1,7] Plasma methoxytyramine was not performed in the present series.

While computed tomography (CT) and magnetic resonance (MR) imaging are accurate for localising intra-adrenal phaeochromocytoma and provide the best anatomical details, they are less helpful in cases of extra-adrenal or metastatic disease. Metaiodobenzylguanidine (MIBG) scintigraphy is advantageous as a whole body screening tool and is more specific than CT/MR imaging. Compared to NAd/Ad-secreting phaeochromocytomas, DA-secreting tumours are less likely to enhance with MIBG, especially the exclusively DA-secreting ones. In Proye's series, the sensitivity of MIBG for DA-secreting phaeochromocytomas was 66%.[14] Similarly, the sensitivity of MIBG in the present series is 60%, much lower than the 86%–90% for NAd/Ad-secreting phaeochromocytomas.[17] MIBG is probably less useful in DA-secreting tumours than in NAd/Ad-secreting tumours due to its relative lack of sensitivity. ^{18}F-labelled deoxyglucose positron emission tomography (^{18}FDG-PET) has been suggested as a complementary modality in the detection of phaeochromocytomas/paragangliomas that are MIBG negative.[17] Octreotide scintigraphy is another potentially effective modality for MIBG negative phaeochromocytomas/paragangliomas, especially the malignant ones. MIBG negative but octreotide positive DA-secreting paraganglioma has been previously reported in the literature.[5]

A definitive treatment for phaeochromocytomas/paragangliomas is en bloc surgical resection. For DA-secreting tumours, an open, rather than a laparoscopic approach, is recommended regardless of the tumour size, owing to the high rate of malignancy.[12] 80% of the patients in the present series underwent surgical resection of the primary tumours. Surgery was incomplete in two cases. Preoperative α-blockade is routinely used in NAd-secreting tumours to prevent a hypertensive crisis during tumour manipulation. However, it is not routinely recommended for DA-secreting tumours due to its association with potential cardiovascular collapse.[12,14] This phenomenon is attributed to the unopposed hypotensive action of DA when the pressor catecholamines are blocked. In the present series, two out of four patients who received preoperative α-blockade developed severe hypotension, and one of them died after a cardiovascular arrest on postoperative Day 1.[2,10-12] For the rest of the patients who were not administered pre-operative α-blockade, only three patients developed hypertension during tumour manipulation, but all were mild and transient, except for one patient who required intraoperative nicardipine infusion to control the blood pressure.[5] Metyrosine, an inhibitor of tyrosine hydroxylase that converts tyroxine to DOPA (the precursor of DA, but with no α-blocking effects), has been advocated in the management of DA-

secreting tumours for symptom control. However, it is not recommended for routine use.[12]

It has been demonstrated that the preferential excretion of DA over NAd/Ad is due to the reduced activity of DA-β-hydroxylase that converts DA to NAd.[6,17] This suggests that DA-secreting tumours are poorly differentiated compared to tumours that secrete NAd/Ad. The malignancy rate reported for DA-secreting tumours is 66%–90%, compared to 21%–29% for NAd/Ad-secreting tumours. Malignant phaeochromocytomas were also found to have higher levels of DA excretion than benign ones.[14,15] DA-secreting malignant phaeochromocytomas tend to have a more aggressive course than NAd/Ad-secreting ones.[15] Five (33.3%) cases in the present series fulfilled the criteria of malignancy. Of these, two cases had a metastatic disease, while the rest had evidence of a local invasion. All cases were extra-adrenal, with a mean tumour size of 15.7 cm. However, the malignancy rate in the present series is only 33.3%. This is probably an underestimation due to the limited duration of follow-up for most cases. Features predictive of malignancy for phaechromocytomas include an elevated urinary DA, extra-adrenal location, large tumour size and abnormal DNA ploidy.[11,17] In view of the high malignancy rate of DA-secreting tumours, lifelong follow-up for recurrence or metastases would be prudent. The differences between DA and NAd/Ad-secreting phaeochromocytomas/paragangliomas are summarised in Table III.

In conclusion, DA-secreting phaeochromocytomas/paragangliomas differ substantially from those that secrete NAd/Ad in the following aspects: (1) There is a lack of a classical presentation of adrenergic excess; (2) they are more likely to be extra-adrenal; (3) they are less likely to enhance with MIBG; and (4) they have higher recurrence and malignancy rates. All these result in delayed diagnosis and a poorer prognosis compared to NAd/Ad-secreting tumours. A high index of suspicion, through the inclusion of urinary or plasma DA in catecholamine screening for all suspected phaeochromocytomas/paragangliomas, is essential. The provision of α-blockade is not recommended routinely, but perioperative haemodynamic instability should be anticipated, as it may have a significant impact on mortality and morbidity. Lifelong surveillance for all DA-secreting tumours for recurrence or metastasis would also be mandatory.

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