CASE REPORT

Catecholamine-secreting paraganglioma: the challenges of perioperative management

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SUMMARY

An asymptomatic 48-year-old man presented with a right-sided neck mass. A CT scan demonstrated a lesion at the carotid bifurcation and an angiogram showed splaying of the carotid arteries. His plasma metanephrines were raised confirming a catecholamine-secreting paraganglioma. Metaiodobenzylguanidine single-photon emission CT showed focal high tracer uptake in the right of the neck. Histology revealed a tumour, arising within a nerve, composed of oval-shaped cells arranged in nested (zellballen) as well as in trabecular patterns. Immunohistochemistry was positive for neuroendocrine markers chromogranin A, synaptophysin and CD56. Preoperative management included an endocrinologist initiating α -adrenergic and β -adrenergic blockers. Intraoperatively, acute hypertension occurred whenever the tumour was manipulated. Close communication between the surgeons and the anaesthetist allowed for these episodes to be predicted and treated with fast-acting antihypertensives such as sodium nitroprusside. Postoperatively, the patient recovered well and his antihypertensives were discontinued.

BACKGROUND

A paraganglioma is a tumour that contains chief cells derived from neural crest (chromaffin) cells. The terms glomus tumour and chemodectoma are synonymous with paraganglioma.

Paraganglia are widely distributed throughout the sympathetic and parasympathetic nervous system. Sympathetic paraganglia are symmetrically distributed along the paravertebral axis from high in the neck, close to the superior cervical ganglion, to the abdomen and pelvis. Parasympathetic paraganglia are localised to the skull base, and head and neck.¹

The largest concentration of paraganglionic cells in the body is located in the adrenal medulla. In this area, they can form pheochromocytomas, which are uncommon. The commonest anatomical location of paragangliomas in the head and neck is the carotid body bifurcation (carotid body tumour), followed by the jugular bulb of the temporal bone (glomus jugulare), promontory of the cochlea (glomus tympanicum), vagal nerve (glomus vagale) and larynx.¹⁻³

The exact function of paraganglia is not clear, except where they act as chemoreceptors sensitive to arterial pH and oxygen tension in the carotid body and aortic arch.² Although all paraganglia have the capability of producing catecholamines, this is relatively uncommon, occurring in up to 4% of head and neck paragangliomas. The majority

secrete norepinephrine; the production of epinephrine or dopamine is uncommon.^{2 4 5} This occurs via the decarboxylation of L-3,4-dihydroxyphenylalanine (DOPA) into dopamine, norepinephrine and epinephrine.²

Up to one-third of head and neck paragangliomas are familial, which equates to an incidence of one in one million people.⁶ Multicentricity is more common in familial,⁷ than in sporadic⁴ paragangliomas. Familial paragangliomas have an autosomal dominant inheritance pattern with maternal imprinting.⁸ There are four types of hereditary paraganglioma. People with types 1 (SDHD gene), 2 (SDHAF2 gene) and 3 (SDHC gene) usually develop paragangliomas in the head or neck region whereas people with type 4 (SDHB gene) usually develop extra-adrenal paragangliomas in the abdomen and are at higher risk for malignant metastasising tumours.^{1 8} Mutations associated with types 1, 3 and 4 affect the enzyme succinate dehydrogenase (SDH), which is involved in the citric acid cycle (Krebs cycle) and oxidative phosphorylation.^{1 8}

Determining the diagnosis of paraganglioma, and whether the lesion is catecholamine secreting, is essential prior to operative intervention. We will discuss the importance of medically optimising a patient preoperatively with the assistance of an endocrinologist, and the intraoperative medical challenges faced by the anaesthetist and surgeon excising a catecholamine-secreting paraganglioma.

CASE PRESENTATION

A 48-year-old man was incidentally found to have a right-sided neck mass following right shoulder dislocation. The patient was asymptomatic and not hypertensive. Examination revealed an isolated mass measuring 4×3 cm located deep to the right of the sternocleidomastoid muscle. The remainder of his examination was unremarkable as was his blood pressure and heart rate. He was otherwise fit and well with no significant medical, social or family history.

INVESTIGATIONS

Contrast-enhanced CT of the neck showed a heterogeneous lesion at the right carotid bifurcation in keeping with a paraganglioma measuring 41×37 mm (figure 1). CT angiogram demonstrated splaying of the internal and external carotid arteries, known as a Lyre sign (figure 2). CT angiography helped map out the arterial and venous blood supply of the tumour, which aided the surgeons. Although it was not performed in this

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Figure 1 Contrast-enhanced CT of the neck (coronal section) demonstrating a heterogeneous lesion at the right common carotid artery bifurcation, measuring 41x37 mm.

patient, digital subtraction angiography (DSA) offers preoperative tumour feeder vessel characterisation and endovascular access for embolisation, which has been reported to reduce blood loss and operative time.² Alternatives for preoperative vessel characterisation include MR angiography (MRA). While MRA may have lower neurological morbidity and mortality

Figure 2 CT angiogram showing splaying of the right internal and external carotid arteries by a lesion at the carotid bifurcation (Lyrer sign).

than DSA, its sensitivity is not high enough to reveal important vascularisation.⁹

The patient subsequently underwent nuclear medicine investigations in the form of metaiodobenzylguanidine (MIBG) iodine-123 single-photon emission CT. This showed focal high tracer uptake in the right side of the neck, consistent with uptake in the known paraganglioma (figure 3). No other abnormal tracer uptake was seen in the neck or the remainder of the body.

Blood investigations revealed a markedly raised plasma normetadrenaline level of 3485 pmol/L (reference range 0–1000 pmol/L) and metadrenaline level of 1467 pmol/L (reference range 0–600 pmol/L). This confirmed the diagnosis of catecholamine-secreting paraganglioma. The remainder of the patient's blood investigations were unremarkable including his full blood cell count, urea, creatinine, electrolytes, corrected calcium, phosphate and liver function tests.

Histopathological assessment of the fully excised surgical specimen confirmed a paraganglioma. It described a well-circumscribed encapsulated tumour arising within a nerve, and composed of oval-shaped tumour cells arranged in nested (zell-ballen) as well as in trabecular patterns (figure 4). The tumour cells contained abundant granular eosinophilic cytoplasm with

Figure 3 Metaiodobenzylguanidine iodine-123 single-photon emission CT showing focal high tracer uptake in the right side of the neck. No other abnormal tracer uptake is seen in the neck or in the remainder of the body.

Figure 4 Histopathological photomicrograph (H&E stain, magnification $\times 40$) showing a tumour arising within a nerve and composed of oval-shaped tumour cells arranged in a nested (zellballen) pattern.

uniform oval vesicular nuclei. Immunohistochemical stains showed that the tumour cell was positive with neuroendocrine markers chromogranin A (figure 5), synaptophysin and CD56. The S100 demonstrated a well-preserved sustentacular network. The MIB 1 was under 1%. Preoperative fine-needle aspiration cytology and open biopsy were not performed due to the hyper-vascular nature of the tumour.

DIFFERENTIAL DIAGNOSIS

Clinically, a paraganglioma (carotid body tumour) presents as a painless, pulsatile, slowly growing neck mass that moves in the anteroposterior or horizontal plane but not in the vertical plane, due to fixation to the carotid bifurcation.¹⁰ It can also have systemic manifestations such as sustained or paroxysmal hypertension, headache, palpitations and sweating, although these were not present in this patient.

Biochemical diagnosis of catecholamine-secreting paragangliomas includes urinary fractionated metanephrines or catecholamines, or, less commonly, high-performance liquid phase chromatography measurements of plasma-free metanephrines.¹¹ In sporadic tumours, the sensitivity and specificity of detecting plasma-free metanephrines is 99% and 89%, respectively.²

Figure 5 Photomicrograph of immunohistochemical staining (magnification $\times 40$) showing that the tumour cell is positive with neuroendocrine marker chromogranin A.

Knowing a tumour's catecholamine status helps the clinician to plan for potential preoperative and intraoperative hypertension. However, preoperative medical therapy does not negate the possibility of acute intraoperative hypertension, as we will describe.

Radiological diagnosis is offered by contrast-enhanced CT (figure 1) which typically shows a hypervascular tumour located between the internal and external carotid arteries. Gadolinium-enhanced T1-weighted MRI is more accurate and may show a *salt and pepper* appearance. The *salt* refers to high-signal subacute haemorrhages and *pepper* to low-signal blood flow voids.¹²

Histologically the tumour is composed of zellballen epithelioid cells in nests separated in a trabecular fashion (figure 4). Immunohistochemical stains may test positive with neuroendocrine markers including chromogranin A¹³ (figure 5), Synaptophysin and CD56 glycoprotein.¹⁴ Diagnosis of malignancy requires the detection of distant metastasis, which is uncommon (around 3%).¹⁵ Histopathology alone is not sufficient.^{1–3} Immunohistochemical staining using MIB 1 monoclonal antibody assesses malignant potential but is not diagnostic.¹⁶

In order to detect metastatic paragangliomas, MIBG iodine-123 scintigraphy (figure 4) can be used.^{1 2 11} The MIBG molecule resembles norepinephrine and is taken up preferentially by adrenergic tissue. Although MIBG scanning is specific (100%), it has a low sensitivity (41.6–60%) in mapping metastatic paragangliomas due to its low spatial resolution.¹⁷ Gadolinium-68-DOTA-octreotate (⁶⁸Ga-DOTATATE) positron emission tomography (PET)/CT scanning has been shown to have higher diagnostic accuracy and sensitivity (80–100%), as well as greater specificity (100%), in mapping paraganglioma metastasis than ¹³¹I-MIBG scintigraphy, contrast-enhanced MRI (sensitivity 63.1%) and fluorine-18 fluorodeoxyglucose PET/CT (sensitivity 66–77.8%).^{17 18}

TREATMENT

Preoperative medical optimisation of the patient by an endocrinologist was started weeks before the operation. This involved initiating α -adrenergic and β -adrenergic receptor blockers anti-hypertensives, namely phenoxybenzamine and propranolol. Phenoxybenzamine is an irreversible non-competitive α -adrenergic blocker acting against presynaptic α_2 receptors and postsynaptic α_1 receptors. Propranolol is a non-selective competitive β_1 and β_2 receptor blockers.

Standard anaesthetic induction and maintenance took place with propofol, atracurium and a remifentanyl infusion. This technique avoided the use of volatile anaesthetic agents, thus minimising catecholamine-induced arrhythmias.¹⁹ A range of antihypertensive agents were prepared in advance of induction to manage potential hypertensive crises, which are most likely to occur following tracheal intubation, tumour manipulation and ligation of the tumour's venous drainage.

OUTCOME AND FOLLOW-UP

Postoperatively, blood pressure monitoring continued for 24 h in a higher dependence setting. The patient was observed for neurological dysfunction, myocardial ischaemia and hypotensive or hypertensive episodes. Postoperative hypotension is a risk due to the reduction in plasma catecholamine levels after secreting tumour removal. Our patient was, however, normotensive, and so his antihypertensives were discontinued on advice of the endocrinologists. Postdischarge, the patient has been well and there has been no recurrence. He is being followed up by endocrinologists and ear, nose and throat (ENT) surgeons to look for metastasis or recurrence.

DISCUSSION

Catecholamine-secreting paragangliomas in the head and neck require multidisciplinary preoperative, intraoperative and post-operative management to reduce serious morbidity and offer potential curative treatment.

Owing to location and catecholamine-secreting properties this paraganglioma may have originated from the sympathetic cervical ganglion rather than the vagus nerve. In terms of antihypertensive therapy, blood pressure optimisation preoperatively may assist in reducing acute intraoperative hypertension during tumour manipulation. Although our patient still experienced acute intraoperative hypertension, we suspect it may have been worse without preoperative medical therapy. It is important to start β -blockade after starting phenoxybenzamine (as the other way around would predispose the patient to unopposed α agonism and increase his risk of myocardial infarction).

In the authors' experience, there is a lag time, from tumour handling to an acute rise in blood pressure, of approximately 1–2 min. The highest recorded blood pressure in our patient was 240/195 mm Hg. During episodes of acute hypertension, the surgeons paused, while the anaesthetist titrated sodium nitroprusside, a vasodilator agent with a rapid onset and offset. It took 1–2 min for the blood pressure to fall to acceptable parameters before the surgeons could resume. This occurred several times. Close and regular communication between the surgeons and anaesthetists during tumour manipulation allowed acute hypertensive episodes to be better predicted and managed.

Learning points

- ▶ Four per cent of head and neck paragangliomas secrete catecholamines, the majority secreting norepinephrine.
- ▶ Preoperative management includes an endocrinologist initiating α -adrenergic followed by β -adrenergic blockers to stabilise the patient's blood pressure.
- ▶ Intraoperative hypertensive crisis can be expected each time catecholamine-secreting paraganglioma is handled.
- ▶ Close and regular communication between the surgeons and the anaesthetist allows for these episodes to be predicted and treated with fast-acting antihypertensives.
- ▶ Catecholamine-secreting paragangliomas require multidisciplinary perioperative management to reduce the risk of serious morbidity or mortality and to offer potential curative treatment.

Competing interests None declared.

Patient consent Obtained.

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