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CASE REPORT

Phaeochromocytoma and Paraganglioma Excision Involving the Great Vessels

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Objective/background: Phaeochromocytomas and paragangliomas are vascular neuroendocrine tumours distributed between the neck and the pelvis and may be associated with catecholamine secretion. The aim of the study was to describe the complex surgical management required to excise these tumours when in close proximity to the great vessels (aorta and vena cava).

Methods: This was a retrospective case series. Patients included those undergoing surgical excision of a phaeochromocytoma or paraganglioma involving the great vessels. Data on clinical presentation; genetic mutations; tumour location; catecholamine/metanephrine secretion; surgical strategy; pre-, intra-, and post-operative course were collated.

Results: Five patients (age range 16–60 years) were identified; three had thoracic paragangliomas located under the arch of the aorta, one had an abdominal paraganglioma invading the aorta, and one had a massive phaeochromocytoma invading the inferior vena cava via the adrenal vein. Three patients had predisposing germline mutations. All patients had adrenergic blockade prior to surgery. A diverse range of complex surgical techniques were employed to excise tumours, including cardiopulmonary bypass, aortic resection, grafting and venotomy of the vena cava. Early post-operative complications were limited.

Conclusions: Excision of phaeochromocytomas and paragangliomas involving the great vessels is high risk surgery optimally undertaken within a multidisciplinary setting in a tertiary referral centre. Comprehensive radiological and biochemical assessment, meticulous pre-operative preparation and close intra- and post-operative monitoring are essential. Radiological imaging may be unable to resolve the tumour extent and anatomy pre-operatively and direct visualisation of the tumour may be the only way to clarify the surgical strategy. Pre-operative knowledge of the genetic predisposition may influence surgical management.

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INTRODUCTION

Phaeochromocytomas are chromaffin cell neuroendocrine tumours of the adrenal medulla. Paragangliomas (PGLs) are extra-adrenal tumours of sympathetic (secretory) or parasympathetic (mainly non-secretory) origin, located between the base of the skull and the pelvis. These highly vascular tumours are, on occasion, positioned in close proximity to the great vessels (aorta and vena cava). Tumour related morbidity and mortality results from associated catecholamine excess; hypertensive crises; cardiovascular sequelae; mass effect and metastatic disease. Approximately 30% of tumours are associated with germline mutations, 30% are associated with somatic mutations, and the remainder appear sporadic.[1,2] Malignancy rates for those with phaeochromocytoma or sympathetic PGLs are estimated to be 17%, although rates are higher with certain germline mutations, for example succinate dehydrogenase B (*SDHB*).[3]

The mainstay of therapy is surgical excision of tumours. When a tumour abuts or invades a great vessel, surgical decision making can be complex. The extent of tumour involvement in surrounding structures; symptoms; comorbidities; local surgical expertise; availability of alternative treatments; and patient preference all need consideration. Non-resectable disease is treated with radionucleotide therapy or chemotherapy.[4] Experience in managing five patients who underwent surgical excision of either a phaeochromocytoma or a PGL involving the great vessels is presented.

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CASE SERIES

Five patients over a 10 year period (2004—13), from a single institution, were identified as having surgical excision of either a phaeochromocytoma or a PGL involving the great vessels (aorta or vena cava). All five had pre-operative alpha- and beta-adrenergic blockade with phenoxybenzamine and propranolol. A summary of presentations and clinical characteristics is given in Table 1, intra-operative surgical data in Table 2, and radiological imaging from cases 2—5 is shown in Fig. 1.

Thoracic PGLs

Three patients had thoracic PGLs (patients 1, 2, and 5). Patient 2 had an *SDHB* mutation and patients 5 an *SDHA* mutation. Aortic transection and cardiopulmonary bypass was required to access the tumours for excision. A median sternotomy was followed by the establishment of cardiopulmonary bypass with aortic and bicaval cannulation and aortic cross-clamping (Fig. 2). Cardioplegia was then established. Following tumour excision, the aorta was re-anastomosed, unclamped, and the patients were taken off cardiopulmonary bypass.

Abdominal PGL invading aorta

Patient 3, an *SDHB* mutation carrier, required excision of the abdominal PGL with resection of part of the infrarenal abdominal aorta, which had been invaded by tumour. The aorta was cross-clamped and then transected. A 16 × 8 mm bifurcated Dacron graft was inserted. An additional nodule beneath but separate from the PGL was also excised and confirmed on histological examination to be a lymph node metastasis.

Phaeochromocytoma invading inferior vena cava

Patient 4, on computed tomographic imaging, was found to have a 8.3 × 9.5 cm ill defined heterogeneous right adrenal mass with a necrotic centre invading the inferior vena cava (IVC) superiorly and displacing the right kidney inferiorly (Fig. 1E, F). Twenty-four hour metanephrines (normetadrenaline and 3-methoxytyramine) were markedly elevated. The metaiodobenzylguanidine (MIBG) scan showed avidity in the tumour but no evidence of distant metastasis. A magnetic resonance scan was able to delineate some of the feeder vessels to the tumour and confirm the IVC invasion in more detail. A MAG 3 renogram demonstrated equal differential function of right and left kidney. It was unclear whether the tumour should be debulked or fully resected. Given the potential requirement for hepatic and IVC resections, surgery was carried out jointly by hepatobiliary and vascular surgeons. Pre-operative coiling was considered but not used as it was unlikely to significantly alter the magnitude of the proposed operations. Endovascular measures such as balloons or stents were precluded owing to the intracaval extension. Direct inspection of the tumour at the time of surgery revealed that the retroperitoneal phaeochromocytoma was infiltrating and displacing the right kidney downwards. It lay behind the right lobe of the liver but did not infiltrate it. A palpable nodule was felt within the IVC and a large number of

Table 1. Patient demographics and disease characteristics.

Patient	Age (y)	Reason for investigation	Germline mutation	Site of phaeo/PGL	Size (cm)	Great vessel involvement	MIBG imaging	FDG PET imaging	Hypertension	Catecholamines 24 h urinary/nmol/24 h			Metanephrines 24h urinary/nmol/24h		
										< 560	< 144	< 3,194	< 2,000	< 4,400	< 2,500
1	60	Hypertension, sweating, and tachycardia	Not done	Thoracic	4.8 × 5.1	Under aortic arch	Avid	—	Yes	3,677	< 30	2,501	—	—	—
2	40	Familial SDHB surveillance	SDHB	Thoracic	5.1 × 3.9	Under aortic arch	Non-avid	Avid	No	356	< 30	2,909	—	—	—
3	16	Familial SDHB surveillance	SDHB	Abdominal	6.5 × 5.4	Invading abdominal aorta	Avid	Avid	No	2,863	57	3,287	—	—	—
4	50	Anaemia investigations	Nil	Right adrenal	12.6 × 7.2	Invading IVC	Avid	—	No	—	—	—	41,481	718	10,011
5	49	Chest pain and exertional shortness of breath	SDHA	Thoracic	5.5 × 3.5	Under aortic arch	Avid	Avid	Yes	—	—	—	11,625	509	15,306

Note. PGL = paraganglioma; MIBG = metaiodobenzylguanidine; FDG PET = fludeoxyglucose positron emission tomography; SDHB = succinate dehydrogenase B; IVC = inferior vena cava; SDHA = succinate dehydrogenase A.

Table 2. Intra-operative surgical data.

Patient	Lesion	Surgery	Surgeon	Duration*	Maximum BP (systolic) mmHg	Minimum BP (systolic) mmHg	Anti hypertensive agents	Vasopressor	Fluid input	Blood loss (mL)	Complications
1	Thoracic PGL	Transection aorta Cardiopulmonary bypass	Cardiothoracic	6h (2 h)	250	61	GTN Esmolol Phentolamine SNP	—	Colloid: 1.5 L RCC: 3 units FFP: 2 units Plt: 1 unit	484	Atrial fibrillation, pericardial haematoma, wound sepsis, AKI
2	Thoracic PGL	Transection aorta Cardiopulmonary bypass	Cardiothoracic	4 h 50 (1 h 35 min)	135	82	GTN Metoprolol Phentolamine	—	Colloid: 1 L RCC: 2 units FFP: 2 units Plt: 1 unit	270	—
3	Abdominal PGL	Transection + resection aorta Dacron graft	Endocrine Vascular	6 h 10 min (50 min)	165	88	SNP Labetolol	Adrenaline Noradrenaline	Colloid: 7 L RCC: 2 units FFP: 2 units Plt: 1 unit	450	—
4	Phaeochromocytoma	Venotomy, excision tumour, IVC repair Right nephrectomy	Hepatobiliary Vascular	3 h 45 min (22 min)	140	80	GTN Labetolol Metoprolol	Noradrenaline	Colloid: 4 L RCC: 4 units (CS 720 mL)	2200	—
5	Thoracic PGL	Transection aorta Cardiopulmonary bypass	Cardiothoracic	6 h (2 h 40 min)	178	62	GTN Labetolol Phentolamine	Noradrenaline	Colloid: 2.5 L RCC: 2 units FFP: 2 units Cryo: 2 units Plt: 2 units	664	—

Note. BP = blood pressure; PGL = paraganglioma; GTN = glyceryl trinitrite; SNP = sodium nitoprusside; RCC = red cell concentrate; FFP = fresh frozen plasma; Plt = platelets; AKI = acute kidney injury; IVC = inferior vena cava; CS = crystalloid; Cryo = cryoprecipitate.

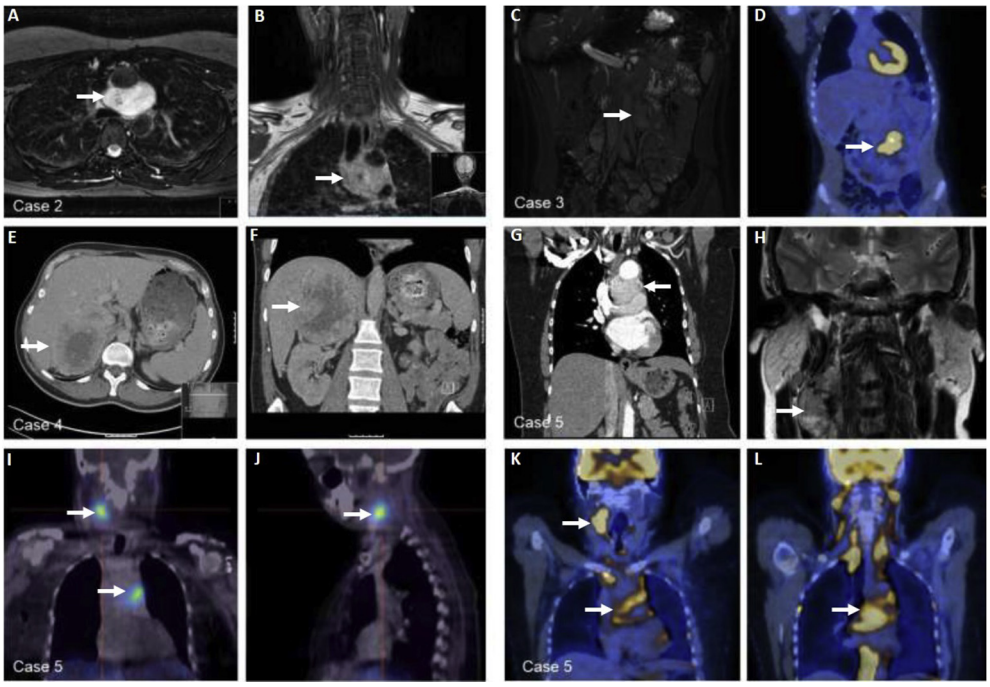

Figure 1. Tumour imaging. Magnetic resonance imaging, fluorodeoxyglucose positron emission tomography (FDG PET), and meta-iodobenzylguanidine (MIBG) imaging of patients 2—5. White arrows indicate tumours. Patient 4 had tumour extending into the inferior vena cava in (E) and (F). (I, J) MIBG imaging of carotid body tumour and thoracic paraganglioma; (K, L) same lesions with FDG PET imaging.

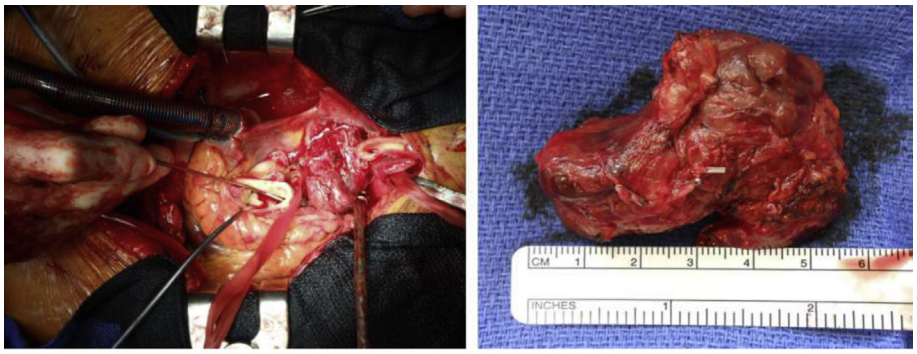

Figure 2. Thoracic paraganglioma excision (patient 5). (A) Sternotomy, transection of aorta and cardiopulmonary bypass. Tumour visible *in situ* (see arrow). (B) Excised thoracic paraganglioma.

veins surrounded the tumour retroperitoneally. Once these vessels were ligated a dissection plane was established around the phaeochromocytoma and the kidney. The right renal vein, artery, and ureter were ligated. Following mobilisation of the right lobe of the liver, the phaeochromocytoma was removed en bloc with the kidney. The retro-hepatic vena cava was then exposed and a longitudinal venotomy was performed to remove a pedunculated 4 × 2 × 3 cm tumour mass along with a patch of wall where it was adherent, at the point of entry of the right adrenal vein. A cell saver was used to retrieve approximately 720 mL red cells. In addition, four units of blood were transfused.

Post-operative outcomes

All patients experienced hypotension (systolic blood pressure 88—62 mmHg), which was corrected with fluid resuscitation and vasopressors in three patients (noradrenaline and adrenaline). Patient 1, with a poor peri-operative health status, experienced intra-operative systolic blood pressure surges up to 250 mmHg and a pulmonary artery wall perforation that required a pericardial patch repair. Patient 4 was shown to have residual disease in the adrenal bed post-operatively and is undergoing adjunctive I^{131} MIBG radionucleotide therapy. The remaining patients have been disease free during follow-up surveillance (range 1—8 years).

DISCUSSION

Despite being one tumour type, the surgical strategy to resect phaeochromocytoma/PGLs can vary significantly depending on tumour location. While the literature includes individual case reports on PGL resection requiring vascular reconstruction, there are no studies documenting the

cumulative surgical experience of managing a series of patients with phaeochromocytomas/PGLs involving the course of the great vessels. Here some of those key aspects are discussed.

Multidisciplinary care

Complex surgery should be undertaken in tertiary referral centres with appropriate multidisciplinary expertise for the diagnostic and pre-operative work-up. A variety of subspecialty surgical teams may be involved depending on the location of the tumour. An anaesthetist with experience of phaeochromocytoma/PGL surgery and a perfusionist to manage either cardiopulmonary bypass and/or the cell saver where there is a potential risk for considerable blood loss is essential. Finally, critical care support in the post-operative period is essential.

Pre-operative assessment

The authors recommend a pre-operative radionucleotide scan (radiolabelled MIBG) and/or fludeoxyglucose positron emission tomography scan to confirm functionality of the tumour and to assess for metastases and coexistent PGLs. A renogram (MAG3) can assess differential renal function if there is concern that a kidney may need to be sacrificed with tumour resection. Some advocate coronary angiography for thoracic PGLs adjacent to the heart to identify tumour feeding vessels.[5] Multidisciplinary review of the various imaging modalities is essential.

Intra-operative strategy

Direct visualisation of phaeochromocytoma/PGLs in close proximity to major vascular structures is an important factor in making decisions about resectability (patients 3 and 4). Radiological imaging may be unable to delineate the extent of tumour infiltration into adjacent structures. During the consenting process patients should be made aware that the surgical strategy may be modified. Surgical preparation for all eventualities is essential.

There is growing evidence that use of a cell saver in cancer surgery is safe. There does not seem to be a greater incidence of haematogenous seeding and subsequent metastases in these patients as suggested by a recent meta-analysis on this topic.[6] At the authors' centre the cell saver protocol includes operations for cancer.

Blood pressure control and adrenergic blockade

Alpha- and beta-adrenergic blockade, in the form of phenoxybenzamine and propranolol prior to surgery, reduces the risk of an intra-operative hypertensive crisis. The risk of post-operative hypotension is also increased as a result of several factors: prior volume depletion by virtue of prolonged catecholamine mediated vasoconstriction of the vasculature; irreversible adrenergic blockade; catecholamine associated cardiomyopathy; the risk of significant intra-operative blood loss; and tumour excision (removal of the source of excess catecholamines). Post-operative hypotension may be relatively resistant to vasopressors and so careful intravascular filling to increase the circulating volume over a 6—8 week period is essential. Cardiomyopathy secondary to catecholamine excess in some reported cases required intra-aortic balloon pump therapy or percutaneous cardiopulmonary support pre-operatively.[7] Cardiopulmonary bypass for thoracic PGL resection allows blood pressure control irrespective of the circulating catecholamine levels or cardiac function.

Vascular reconstruction

In cases where there is direct tumour invasion into a major vessel, resection with wall repair or the insertion of a graft may be needed. PGL resection has been described with grafting of the abdominal aorta, IVC, and superior vena cava. Dacron grafts have been used for aortic and caval grafting along with polytetrafluoroethylene grafts and Gore-Tex® conduits for the vena cava.[5,8] Re-implantation of visceral vessels may be required. Post-operatively, patency of venous grafts may be confirmed by venography and colour flow Doppler.[8]

Genetics

Knowledge of the underlying genetic predisposition prior to surgery may also influence the surgical strategy. Phaeochromocytomas and PGLs associated with mutation in *SDHB* are associated with a high risk of future metastasis (30%).[9] In these patients early surgery to ensure complete resection is essential, for example patient 3. Where mutations are associated with lower metastatic rates, surgical decision making is based on local tumour mass effect, catecholamine excess, the future risk of tumours, and the potential need for multiple surgical resections over time, within the same surgical field. Turnaround times for genetic testing may vary and thus delaying surgery pending a genetic result is not advocated.

CONCLUSION

Phaeochromocytomas and PGLs involving the great vessels present a considerable management challenge with surgery offering the only possibility of cure. Comprehensive pre- and intra-operative preparation is essential, but the final surgical strategy often requires direct visualisation of the tumour where radiological examination is unable to delineate the tumour anatomy. Germline associated disease requires further consideration of the need for multiple operations and the variable risk of malignancy. These patients benefit from management in tertiary centres by multidisciplinary teams well versed in managing the disease and its potential complications.

CONFLICT OF INTEREST

None.

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