Perioperative management for resection of a malignant non-chromaffin paraganglioma of the bladder

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The perioperative management of a 39-year-old patient with a rare, catecholamine producing, non-chromaffin paraganglioma of the bladder is presented. Although the management of this patient was comparable with a patient with a phaeochromocytoma, this case was complicated by marked release of catecholamines, high requirements for vasodilator therapy preoperatively, the presence of a malignant tumour with metastases and an atypical presentation. Preoperatively the diagnosis was a non-metastatic bladder phaeochromocytoma and the blood pressure was controlled with prazosin, nifedipine and propranolol. Anaesthesia was induced with fentanyl, lidocaine, thiopentone and vecuronium and was maintained with nitrous oxide, isoflurane, fentanyl and vecuronium. The patient was haemodynamically stable throughout the operative and postoperative period.

Key words
ANAESTHESIA: evaluation, preoperative; ANAESTHETICS, VOLATILE: isoflurane; PHARMACOLOGY: nifedipine; SURGERY: paraganglioma, phaeochromocytoma; SYMPATHETIC NERVOUS SYSTEM: alpha-adrenergic antagonists, beta-adrenergic antagonists, pharmacology, catecholamines, epinephrine, norepinephrine.

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Paragangliomas arise from a widely disseminated system of small sensory and neurosecretory organs that develops in fetal life and subsequently decreases in size.[1] Phaeochromocytomas are classical examples of endocrinologically active chromaffin paragangliomas. Typical non-chromaffin paragangliomas (NCPG) are tumours of the carotid body and glomus jugulare. A NCPG is usually endocrinologically inactive, but there are rare cases, such as the one described in this report, of a NCPG producing and releasing catecholamines.[2,3]

Urinary bladder paragangliomas are uncommon,[1] have a familial tendency[4] and a mean age of presentation of 38 years. When these paragangliomas stain chromaffin-positive and are endocrinologically active, they have been called bladder phaeochromocytomas. Patients with these "phaeochromocytomas" may present with a classical triad[5] of haematuria, hypertension and micturitional attacks typical of a "phaeochromocytoma syndrome"[6] (headaches, tremulousness, anxiousness and a pounding sensation). Fortunately, bladder phaeochromocytomas are rare, representing only 0.06 per cent of bladder tumours.[2] Seven to 20 per cent of these tumours are malignant[1,5] and can be detected by increased serum dopa and dopamine levels.[7]

In this report, we describe the anaesthetic management of a patient who underwent incomplete resection of a malignant, highly functional NCPG of the bladder. This tumour, which to the best of our knowledge has never been reported before, is difficult to distinguish from a phaeochromocytoma. The case was complicated by atypical presentation, substantial release of catecholamines from the tumour, difficult preoperative control of hypertension and complex surgical resection.

Case report

A 39-year-old, 61 kg, white male was admitted to the urology service with weight loss, nausea, vomiting, malaise, headaches, hypertension, bladder mass, right flank pain and right hydronephrosis. On examination he was cachectic, hypertensive (BP 250/140 mmHg),

tachycardic (HR 120 min^{-1}) and had papilloedema. The cardiologist did not suspect a catecholamine-producing tumour and suggested that the elevated blood pressure was likely secondary to hydronephrosis. Initially, the patient was treated with intravenous fluids, nitropaste (2 in. q6h) and nifedipine (10 mg q6h). Because the patient required better control of his hypertension, captopril was added to his therapy and a diagnostic cystoscopy with bladder biopsy was delayed.

Nitropaste and captopril failed to control the patient's blood pressure. Prazosin was started and the dose was increased gradually to 5 mg PO q6h and the dose of nifedipine was increased to 30 mg PO q4h. With effective control of his blood pressure (150/90 mmHg) the papilloedema resolved. His heart rate, which had remained at 120 min^{-1}, was reduced to 100 min^{-1} with propranolol (10 mg PO b.i.d.). Preoperative investigations included a negative MIBG (meta-iodobenzylguanidine) scan, urine VMA (vanillyl-mandellic acid) 23.8 $mmol \cdot ml^{-1}$ (normal < 3.5 $mmol \cdot ml^{-1}$), urine metanephrines 3.3 $mmol \cdot ml^{-1}$ (normal < 0.5 $mmol \cdot ml^{-1}$) and fasting blood sugar 7.8 $\mu mol \cdot ml^{-1}$. Preoperative diagnosis was a non-metastatic phaeochromocytoma of the bladder.

On the day of the operation the patient was given lorazepam 3 mg sublingually, morphine 7.5 mg intramuscularly and his antihypertensive medications. Before induction of anaesthesia arterial and Swan-Ganz catheters were inserted under local anaesthesia and haemodynamic variables were: cardiac output 7.2 $L \cdot min^{-1}$, systemic vascular resistance (SVR) 1100 $dynes \cdot sec \cdot cm^{-5}$, systemic blood pressure 160/90 mmHg, pulmonary artery blood pressure 26/10 mmHg, and heart rate 105 min^{-1}. Anaesthesia was induced with fentanyl (3 $\mu g \cdot kg^{-1}$), lidocaine (1.5 $mg \cdot kg^{-1}$), thiopentone (200 mg titrated) and vecuronium (7.5 mg). Tracheal intubation was performed after complete muscle relaxation and during cardiovascular stability.

Anaesthesia was maintained with isoflurane, nitrous oxide (50 per cent), vecuronium and small doses of fentanyl (total 4 $\mu g \cdot kg^{-1}$). There were minimal haemodynamic fluctuations during tumour manipulation and surgical stimulation. The tumour was malignant and locally metastatic so a partial cystectomy with pelvic lymphadenectomy, re-implantation of the right ureter and debulking was performed. During the procedure, the patient required gradually increasing isoflurane concentrations to maintain a normal blood pressure. Towards the end of surgery the SVR had increased to 1400 $dynes \cdot sec \cdot cm^{-5}$, so a nitroprusside infusion was begun and the patient was given three 1 mg doses of phentolamine intravenously. The intraoperative blood loss, 3 L, was replaced as it occurred and 8 L of crystalloid were given during the operation. Postoperatively the patient was transferred to the Intensive Care Unit, gradually weaned from ventilator support and his oral antihypertensive agents restarted. The remainder of his hospital course was uneventful.

TABLE Perioperative catecholamine concentrations

Sample	*Norepinephrine* $ng \cdot L^{-1}$†	*Epinephrine* $ng \cdot L^{-1}$‡
Pre-induction	84,900	4,800
Induction	75,400	N.D.*
Incision	72,800	N.D.
Tumour manipulation	53,700	N.D.
Tumour manipulation	57,700	8,100
Tumour excision	69,300	3,500
Tumour excision	77,900	3,200
Closure	85,500	N.D.

*The minimum level of quantitative sensitivity for this assay is 500 $ng \cdot L^{-1}$ with a coefficient of variation of 6.8 and 8.9 per cent for norepinephrine (NE) and epinephrine (E), respectively. Normal human NE and E levels are 42 $ng \cdot L^{-1}$ and 200 $ng \cdot L^{-1}$, and these values double if the patient is hypertensive.
†1 ng = 5.92×10^{-9} mol.
‡1 ng = 5.46×10^{-9} mol.

Perioperative arterial blood samples (5 ml) were obtained for determination of plasma catecholamine concentrations by high pressure liquid chromatography and electrochemical detection with 3,4-dihydroxybenylamine as an internal standard (Table). Blood samples were obtained after informed, written patient consent.

The tumour's pathologic diagnosis was a malignant, metastatic non-chromaffin paraganglioma of the bladder. This was based upon the tumour's histologic features, the clinical data documenting severe hypertension and elevated catecholamines and the presence of metastases within obturator and iliac lymph nodes.

The patient has been followed for a year and has received 13 courses of chemotherapy. His norepinephrine levels have improved but have not reached normal. He still has a pelvic mass.

Discussion

Preoperative diagnostic tests that are used to confirm catecholamine-producing tumours include urinary catecholamines, VMA, and metanephrines (which have high false negative rates[3]), the more accurate plasma catecholamine levels,[3] the glucagon provocation test[3] and the clonidine suppression test.[8] The results of preoperative CT scan, MIBG scan[9] and serum dopa and dopamine levels are used to assess for metastases, malignancy, tumour size and location. In this case surgical exploration revealed local metastatic lesions that were not detected by the MIBG scan. Serum dopamine concentrations were not determined.

Preoperative treatment may consist of alpha-blockers,[10–13] beta-blockers,[14] combination alpha,beta-blockers,[15] calcium channel blockers,[16–18] inhibitors of catecholamine synthesis[13] and magnesium sulfate.[19] In this case, prozosin, a selective $alpha_1$-antagonist was started at the recommended 0.5 $mg \cdot day^{-1}$, but had to be increased to an impressive 20 $mg \cdot day^{-1}$. Propranolol was then used for beta-blockade, although more selective $beta_1$-antagonists, such as esmolol and metoprolol, might avoid the increase in SVR seen with $beta_2$-blockade. Preoperative beta-blockade in patients with catecholamine-producing tumours is controversial and should only be established after treatment with an alpha-antagonist. In addition to high doses of prazosin, our patient required nifedipine at doses 50 per cent greater than the manufacturer's maximum recommended dose. Nifedipine is a potent vasodilator and it may suppress catecholamine release.[16] The ineffectiveness of nitropaste and captopril to control hypertension and the impressive requirements for prazosin and nifedipine are consistent with the high concentrations of plasma catecholamines observed in this patient. The norepinephrine levels in this patient were one hundred times normal baseline values[6] and at least ten times the average baseline values of several groups of patients with phaeochromocytomas as determined by several other investigators.[3,8,14,20]

A patient similar to the one in this case report might benefit from extensive monitoring inserted before induction of anaesthesia because of potential asymptomatic ventricular dysfunction and myocardial ischaemia.[21] Several anaesthetic techniques have been used during resection of catecholamine-producing tumours and no single technique has been clearly identified as superior. The choice of agents should be based on an understanding of the pathophysiology and principles of management of the patient's disease. The use of inhalational and intravenous anaesthetic agents, antiarrythmic drugs and muscle relaxants has been discussed previously.[12,22–24]

Intraoperative problems that could have occurred in this case include poor control of tumour catecholamine release (due to complex venous return), marked blood loss during dissection of the extensive tumour, release of catecholamines from initially undetected metastases and intraoperative hypertension induced by noxious stimuli and/or tumour manipulation. If these potential problems had occurred, we would both treat the cause and, based upon our haemodynamic monitoring, initiate therapy with fluids (crystalloids and blood products) and short-acting vasoactive agents (phenylephrine or nitroprusside) as indicated. The effect of noxious stimuli was minimized by deep anaesthesia with isoflurane. Adequate alpha-blockade may decrease fluctuations due to catecholamines released from the tumour during manipulation. The stable catecholamine concentrations observed during tumour manipulation may be the result of gentle handling and early control of the tumour's blood supply.

It should be noted that surgical intervention was contemplated early in this patient's management because the cardiologist suspected the hypertension was due to hydronephrosis. Surgery was delayed because of a poor response to antihypertensive therapy. In retrospect it is fortunate that immediate surgery was delayed because (1) bladder biopsy may have been misleading if chromaffin staining had been equated with catecholamine production, (2) treatment of the hydronephrosis would not have alleviated the hypertension, and (3) the delay allowed time for a complete investigation and adequate preparation of the patient.

In summary, the successful perioperative management of a patient who underwent incomplete resection of a rare, malignant, highly functional NCPG of the bladder with metastases has been presented. Blood pressure was controlled preoperatively with prazosin, nifedipine and propranolol. Isoflurane, nitrous oxide, vecuronium and small doses of fentanyl provided cardiovascular stability throughout surgery and there were no major fluctuations in plasma catecholamine concentrations.

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Résumé

La conduite periopératoire chez un patient âgé de 39 ans atteint d'un paragangliome non-chromaffine produisant des catécholamines de la vessie est présentée. Même si la conduite chez ce patient était comparable à un patient atteint de phéochromocytome, ce cas fut compliqué par une libération marquée de catécholamines, nécessitant de fortes doses de vasodilatateur en période préopératoire, la présence d'une tumeur maligne avec métastases et une présentation atypique. En période préopératoire le diagnostic était un phéochromocytome non-métastatique de la vessie et la pression artérielle fut contrôlée par la prazosine, nifédipine et propranolol. L'anesthésie fut induite avec le fentanyl, lidocaïne, thiopenthone et vécuronium et était maintenue avec protoxyde d'azote, isoflurane, fentanyl et vécuronium. Le patient était stable hémodynamiquement à travers la période opératoire et en période postopératoire.