Paraganglioma review: A clinical case

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SUMMARY

Introduction: Paragangliomas are rare neuroendocrine tumours that can release catecholamines giving place to hypertensive crises and arrhythmias. Haemodynamic instability suppose a challenge for anaesthesiologists.

Clinical case: 54 years old woman scheduled for resection of a mediastinal paraganglioma located between vital structures. α-blockage was prescribed before surgery. Advanced monitoring was made during anaesthetic management. Extracorporeal circulatory support was necessary due to the haemodynamic instability and location of the tumour near vital structures.

Discussion: We present a review about general management in paragangliomas, focusing on anaesthetic monitoring. The mediastinal location of the tumour requires a special evaluation of the airway and the possibility of extracorporeal assistance.

Conclusion: Paraganglioma surgery requires advanced monitoring and knowledge of physiopathology to reduce the mortality and morbidity.

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1. Introduction

Paragangliomas are tumours arising from the neural crest located in extra-adrenal locations. They are derived from chromaffin cells, so it may be secretory tumours of catecholamines, giving rise to hypertension crisis and arrhythmias triggered by a massive release of these substances. Added to this, secondary symptoms to the location and compression of surrounding structures to the tumour occur; that it may be vitally important in the case of mediastinal locations. The frequency of these tumours is low and therefore the literature available and updated is scarce. However, advances in the preoperative management of these patients and the progress in anaesthesia have led to a reduction in the morbidity and mortality from this type of pathology.

Therefore, we present a review of the anaesthetic and perioperative management of pheochromocytomas and paragangliomas, following a report of a clinical case scheduled for surgery in our hospital.

2. Clinical case

A 54 year-old woman, weight: 66 kg, height: 170 cm, with a history of primary hyperparathyroidism, hypothyroidism and colloid breast tumour operated on in 2002. Her regular treatment was vitamin D and levothyroxine. She started having symptoms of hot flushes for 2–3 min accompanied by palpitations without objective hypertension. Given the patient’s history of hyperparathyroidism, a primary study was conducted to calculate the quantity of catecholamines in her blood and urine fractionated metanephrines. There was an elevation of dopamine (407 ng/L; normal range: <85) and noradrenaline (941 ng/L; normal range: 420) in the blood, and an elevation in 24 h urine of norepinephrine (206 mg; normal range: 23e105), dopamine (838 mg; normal range: 190e450) and adrenaline (22 mg; normal range: 4e20). PTH, calcium and phosphorus levels were also high.

A cervical-thoracic-abdominal CT was performed and it identified a mediastinal mass, high uptake, of 7/6 cm that compresses the left main bronchus and presented a plane of cleavage between the aorta and vena cava. In the chest CT study, contrast was observed in the separation plane of the mass within the main pulmonary artery and pulmonary arteries. The mass presents extensive mediastinal, paratracheal, para-aortic, left hilar and subcarinal circulation (Fig. 1).

After the diagnosis, the patient was scheduled for surgery and hospitalized to receive alpha-blockage therapy prior to surgery. An initial dose of phenoxybenzamine 10 mg, was administered 3 times a day. Arterial pressure values remained stable between 130 – 98/65–46 mmHg with a heart rate between 69 and 102 bpm.

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Full body metaiodobenzylguanidine scintigraphy was performed. There was intense fixation on the mediastinal mass that obstructs output of the left main bronchus. There were no other locations suggestive of metastasis (Fig. 2).

Fibrobronchoscopy revealed an extrinsic compression in the anterior and posterior side of the carina with revascularization in the anterior mucosa without any signs of infiltration being performed. Pulmonary function tests have a result of FVC: 115%; VEMS: 120% and the Doppler echocardiography showed normal values and limits to rule out pulmonary hypertension.

Prior to surgery, catheterization of both the subclavian arteries, showed hypertrophy of both thyrocervical trunks with vascular branches of the pathological aspect (Fig. 3). An embolization of the right thyrocervical trunk with particles of 500–1200 microns and 2 coils was performed to reduce intraoperative bleeding. During the embolization of the left thyrocervical trunk, the patient reported episodes of headache and loss of vision so the embolization was stopped.

The patient progressively recovered vision and a brain CT was performed. There was no evidence of acute or subacute brain injury.

2.1. Surgical and anaesthetic management

The night before the intervention, 10 mg of diazepam (oral) and premedication with 2 mg of midazolam (intravenous) were administered before entry to the operating-room. At anaesthetic induction, the patient was preoxygenated for 5 min with \( \text{FiO}_2 \) 100%. 150 μg of fentanyl, 150 mg of propofol and 50 mg of rocuronium were administered. By direct laryngoscopy, orotracheal intubation was performed. There was no episode of haemodynamic instability during induction.

Mechanical ventilation in volume control with the following parameters: Tidal volume: 450 ml; FR: 12 rpm; PEEP: 5 cmH2O; \( \text{FiO}_2 \): 50%. Peak airway pressure: 22 cmH2O and plateau pressure: 18 cmH2O. The patient maintained 100% saturation after anaesthetic induction.

We proceeded to invasively monitor blood pressure by catheterization of the left radial artery and haemodynamic monitoring using the advanced ProAQT® monitor Pulsion Medical Systems (Fig. 4).

Two peripheral venous catheters 18G and a central via jugular right were used due to the surgical risk and likely intraoperative drug delivery. The initial parameters were: IC 2.7 L/min/m², VVS: 7%, VPP: 8%, RVS: 1100 dyn s cm5/m², SVI: 40 ml/m².

The right radial artery was also catheterized due to the possibility of doing an antegrade cerebral perfusion if the surgeon needed to clamp the supra-aortic trunk during the cardiopulmonary bypass.

During maintenance of anaesthesia, we used intravenous therapy with propofol at doses 2–3 mg/kg/h, rocuronium 0.3 mg/kg/h and remifentanil 0.1–0.2 mg/kg/min.

The anaesthetic depth was monitored using the bispectral index (BIS) which maintained values between 35 and 55 (Fig. 4).

At the beginning of surgery the patient remained haemodynamically stable, maintaining values of IC: 3.5–4.5 L/min/m², HR: 70 bpm; PA 100/60 mmHg; VVS: 10%; RVS: 1000 dyns cm5/m².

To control arrhythmias and possible hypertensive crisis during surgery, drugs such as urapidil, esmolol, phentolamine and nitroglycerin were prepared.

As the surgery advanced, manipulation of cardiac structures was required. The tumour was placed around the aortic arch (shaped like an hourglass) and the pulmonary artery and dorsal trachea were compressed. Hypotension episodes in relation to the mobilization of cardiac structures were recovered with administration of phenylephrine dose 100–200 μg and momentary detention of the manipulation of the heart. Because of the haemodynamic instability it was decided to initiate extracorporeal circulatory support without cardiac arrest.

Cerebral oximetry monitoring was performed by the NIRS (Non-invasive Near Infrared Spectroscopy) SOMANETICS INVOS 5100c® monitor. During the period of haemodynamic instability, oximetry presents values between 45/50 that were recovered after reaching haemodynamic stabilization (Fig. 5).

The estimated blood losses were 1200 ml. It transfused four red blood cell concentrates, one concentrate of plasma and 1 g of...
tranexamic acid. Entries of crystalloids were 4000 ml and outputs were 1300 ml. The VVS was maintained around 15 - 10% and the IC did not decline from 3 L/min/m². During the intervention serial arterial blood gas analyzes were performed, being haemoglobin values greater than 8 g/dl, Lactic less than 1.7 mmol L⁻¹. The extracorporeal circulation time was 47 min.

Haemodynamically, the patient presented punctual problems of hypotension but did not evidence any episode of hypertensive crisis or arrhythmias.

The duration of intervention was 6 h. We transported the patient to the Critical Care unit, under the influence of sedation. Sedation was maintained for 4 h to completely replace the volume, body heating and alveolar recruitment. After objective clinical stability, sedation was removed. The patient was conscious and oriented, responding to commands and effective spontaneous ventilation so it was decided to extubate the patient.

The pathology report confirmed it was a mediastinal paraganglioma that occupied the entirety of the piece removed at surgery.

3. Discussion

Extra-adrenal paragangliomas are rare tumours that arise from the neural crest tissue chromafﬁn cells and becomes parasympathetic and sympathetic paraganglia throughout the body. The incidence of pheochromocytoma is 2–8 million people per year.¹

25% of pheochromocytomas and extra adrenal paragangliomas can be present as part of a hereditary syndrome like: MEN 2A, MEN 2B (Multiple Endocrine Neoplasm which includes medullary thyroid cancer, pheochromocytoma and hyperparathyroidism), Von Hippel-Lindau disease, Neurofibromatosis Type I and hereditary paraganglioma syndrome.²

The neural crest tissue becomes parasympathetic and sympathetic paraganglia. The sympathetic paraganglia includes the adrenal medulla, the organ of Zuckerkandl near the aortic bifurcation and other paraganglia along the distribution of the sympathetic nervous system Fig. 6.³

The parasympathetic paraganglia includes the carotid glomus and other paraganglia cervical and thoracic branches of the vagus and glossohyparyngeal nerves.

The term pheochromocytoma is used exclusively for tumours arising from the adrenal medulla and extra-adrenal paraganglioma for similar tumours that arise in other locations. Amongst the possible locations of extra-adrenal tumours, the mediastinal location involves serious symptoms and is life threatening due to the proximity to large aortic vessels and the primary tracheobronchial structures.

Patients may have symptoms secondary to compression of structures close to the tumour: dyspnoea, dysphagia, Horner’s syndrome, syndrome of the superior vena cava, vocal cord paralysis, or paralysis of the phrenic nerve.

Pheochromocytoma and extra-adrenal sympathetic paraganglioma patients may have the symptoms of excess production of catecholamine such as: hypertension, headache, sweating, vigorous palpitations, tremor and facial pallor. These symptoms are often paroxysmal, although hypertension sustained between paroxysmal episodes is reported in 50–60% of patients with pheochromocytoma. Hypertension episodes can have variable frequency, severity, and duration, and are often extremely difficult to clinically control.

A severe discharge of catecholamines can lead to hypertension crises, cardiac arrhythmias, myocardial infarctions or even death.⁴

The symptoms triggered by an excess of catecholamines can be spontaneous or induced by a variety of situations, including the following: strenuous physical activity, trauma, labour and delivery, induction of anaesthesia, surgery or other invasive procedures such as the direct manipulation of the tumour.

3.1. Diagnosis

The biochemical diagnosis of a tumour derived from catecholamine secreting chromaffin cells is performed by measuring plasma or urine catecholamines and fractionated metanephrine.⁵
The location of the tumour is diagnosed by computerized tomographic (CT) or magnetic resonance imaging (MRI). I23I metaiodobenzylguanidine scintigraphy (MIBG) accompanied by CT imaging, provide anatomical and functional information with good sensitivity (80–90%) and specificity (95–100%).

There are study groups that correlate the concentration of catecholamines and metanephrines in urine, with the high likelihood of hypertensive crises occurring during surgery.

### 3.2. Treatment prior to surgery

Surgical treatment is indicated for the cure of this type of tumour. Prior to surgery, we performed pharmacological treatment in order to control the postoperative arrhythmias, heart rate, and hypertensive crisis, as well as allowing for a restoration of the intravascular volume. A reduction in mortality was observed from 60 to 40% up to 0–6% after the introduction of preoperative α-blockade in this type of patient medication.

Phenoxybenzamine is a non-competitive α antagonist, used since 1950 for the control of blood pressure in patients with pheochromocytoma. It starts with an initial dose of 10 mg/day by oral administration and increasing the dosage according to the blood pressure control and up to 80/100 mg/day. Blockage of both α1 and α2, interrupts the self-regulation of the sympathetic system by α2 receptors, consequently, the response to an excessive production of catecholamines has to be controlled by β-antagonists (Table 1).

Prazosin and doxazosin are selective α1-antagonists. Since no receptor α2 is antagonized, use of the β-Blocker is reduced. β-receptor antagonists were used to control tachycardia and arrhythmias induced by tumour secretion of norepinephrine and dopamine. The drugs used were β1-selective antagonists such as atenolol (100 mg/day) or bisoprolol (10–20 mg/day). Also used were non-selective β antagonists such as propranolol (40–240 mg/day), avoiding its administration in patients of obstructive lung diseases.

Realization of β blockade prior to α antagonism is contraindicated, due to the risk of triggering a serious hypertensive crisis, being blocked vasodilation capacity of β receptor.

### 3.3. Preoperative embolization

Neuroendocrine tumours have a high pathological vascularization that can complicate the process of tumoural resection. Intraoperative blood loss may worsen the clinical situation which is already altered due to the secretion of catecholamines and adrenergic blockage. Embolization of tumour vessels before surgery is indicated to reduce the intraoperative bleeding.

### 3.4. Anaesthetic management

The intraoperative management of neuroendocrine tumours secreting catecholamines poses a challenge for the anaesthesiologist because of haemodynamic lability, and the release of catecholamines during surgical manipulation that can trigger a hypertensive crisis, tachycardia and severe arrhythmias in a matter of seconds. Therefore a correct knowledge of haemodynamic monitoring and pharmacological management are essential in such cases.

These patients have a state of hypovolaemia due to sustained vasoconstriction of tumour catecholamines. Orthostatic hypotension is common in these patients. A correct premedication with alpha blockers can correct hypovolaemia and episodes of orthostatic hypotension are lower in frequency.

Situations of hypertensive crisis, defined as SBP > 180, and arrhythmias can be solved by using direct vasodilators and beta blockers with a short onset time action and a short half-life.

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**Table 1**

<table>
<thead>
<tr>
<th>Receptor</th>
<th>Effect</th>
<th>Catecholamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>α 1</td>
<td>Vasoconstriction (venous &amp; arterial), intestinal relaxation, stimulation of glycogenolysis, uterus contraction, mydriasis.</td>
<td>Norepinephrine</td>
</tr>
<tr>
<td>α 2</td>
<td>Inhibition norepinephrine presynaptic release, vasoconstriction, lowering insulin release, sedation.</td>
<td>Epinephrine and norepinephrine</td>
</tr>
<tr>
<td>β 1</td>
<td>Positive chronotropy and inotropy, stimulation renin release, lipolysis.</td>
<td>Epinephrine and norepinephrine</td>
</tr>
<tr>
<td>β 2</td>
<td>Muscle vasodilatation, bronchodilatation.</td>
<td>Epinephrine</td>
</tr>
</tbody>
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![Fig. 6. Langman's Medical Embriology.10th Edition.](http://dx.doi.org/10.1016/j.tacc.2014.06.002)
3.4.1. Nicardipine

An intravenous calcium antagonist derivative from dihydropyridine. Starts 5 mg/h dose response function, 25 mg/h every 5 min increased to a maximum dose of 15 mg/h.\(^1\)

3.4.2. Urapidil

A vasodilator with a dual mechanism of action: antagonist of alpha – 1 adrenergic receptor postsynaptic peripheral and central level, produces stimulation of the serotonergic 5-HT receptors. Clinically, this effect leads to a decrease in systolic and diastolic blood pressure without any reflex increase in the heart rate. The arterial pressure is decreased at the expense of the systemic vascular resistance, cardiac output unchanged. The initial dose for adults is 25 mg in 20 s, repeat dose every 5 min and if blood pressure control is not achieved, continuous perfusion can be started.\(^1\)

3.4.3. Nitroglycerin

Arteriolar and venous powerful, with greater effect in the territory venous vasodilator. Clinically produces decreased preload, cardiac output and cerebral and coronary vasodilatation. The initial dose for hypertensive crisis is 25 mg/min and can be increased to 25 mg every 5 min until tension control artery. The time of onset is intravenously 1–2 min and duration of 10 min. It may cause hypotension and reflex tachycardia, and caution should be exercised in patients with ischaemic heart disease and heart failure.

3.4.4. Sodium nitroprusside

A potent non-selective peripheral vasodilator, both arterial and venous. Reduces blood pressure as a result of arterial and venous relaxation. The phenomenon of “coronary steal” can occur by decreasing the resistance of vessels and non-ischaemic flow redistribution at the expense of ischaemic areas. The initial dose is 0.5 mcg/kg/min and should be gradually increased depending on the clinical response and magnitude of the hypotensive effect desired. The time of onset of action is 1–2 min.

3.4.5. Phentolamine

This is an alpha – adrenergic blocking agent indicated for the management of hypertensive crises induced by catecholamines. It is intravenously administered via a bolus of 5–10 mg.

3.4.6. Esmolol

This is an adrenergic beta-blocking agent with an extremely short half-life (<10 min). The recommended starting dose is 0.5–1 mg/kg followed by an infusion of 50–200 μg/kg/min.\(^1\)

3.4.7. Propranolol

A non-selective adrenal receptor antagonist β1 and β2. Reduces heart rate and cardiac output. Time of onset and duration 2 min 1–6 h. The hypertensive crisis starting dose is 0.5–3 mg/kg, every 2 min up to a maximum of 6–10 mg. It should not be used in patients with asthma or other obstructive diseases because of the risk of bronchospasm.

After tumour resection, a period of sustained hypotension whose duration can be between 24 and 48 h occurs, and is very common in patients who were premedicated with phenoxybenzamine. Responds to the administration of volume.

3.5. Airway valuation

Possible symptoms of mediastinal tumours are those secondary to compression or obstruction of the airway. Dysphonia, dysphagia, orthostatic dyspnoea or stridor are signs and symptoms that should make us anticipate a possible complication during intubation of the patient. In response to a possible complication during intubation we must consider a spontaneous induction and intubation with fibrobronchoscopy. Induction in a semi-sitting position and postural changes to the lateral and prone position may help prevent tumour obstruction of the airway.\(^9,\(^20\)

3.6. Intraoperative monitoring

In prolonged surgery with high haemodynamic lability, high blood loss, continuous and advanced haemodynamic monitoring during intervention is highly justified. Systems to calculate the stroke volume variation and cardiac index by analysis of pulse wave or by thermodilution are tools that provide information to the anaesthesiologist and guide us in the requirements of fluid therapy or vasoactive amines in situations of haemodynamic instability. In this way we will avoid the deleterious volume overload, or employment of amines in situations of intravascular depletion.\(^1,\(^2\)

Similarly, brain monitoring by measurement of cerebral oximetry systems, indicated in surgery where cerebral circulation may be compromised, will allow us to detect early thromboembolic events and avoid a cerebral hypoperfusion.\(^23,\(^24\)

3.7. Extracorporeal circulation

Due to the location of mediastinal paragangliomas around vital vascular structures and myocardia the technical preparations for surgery should be considered carefully by the various specialists involved. The surgeon may require circulatory assistance to complete an excision with clear margins. In addition, bypass can be supportive treatment in cardiogenic shock that is refractory to vasoactive drugs.\(^25\) It is recommended to have present a cardiovascular surgery team and to have prepared the technical means for circulatory assistance if necessary.\(^26–\(^29\)

4. Conclusion

The low frequency of these tumours and acute events resulting from the massive secretion of catecholamines or compression of vital structures requires a high level of attention by the anaesthesiologist and knowledge of the possible complications and drugs to maintain haemodynamic stability of the patient.

We must insist on correct monitoring to help us limit the aggression of surgery and resection of the mediastinal paraganglioma.

The mediastinum location requires careful patient preparation and planning of the anaesthetic-surgical procedure with a multi-disciplinary approach to the process and collaboration of several specialists as in our case.

Conflict of interest

There is no conflict of interest.

References