Anesthetic Management in Unexpected Extra-Adrenal Pheochromocytoma Presenting with Thoracic Spinal Cord Compression.

A case report

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A 52 year-old female presented with a thoracic paravertebral tumour causing spinal nerve root compression and lower limbs neurologic symptoms. The patient was scheduled to undergo thoracic decompression laminectomy and instrumentation. Markedly severe hemodynamic fluctuations happened during the manipulation of the tumor and continued after the tumor was removed. After multimodal antihypertensive therapy the vital signs were adequately managed and the surgery was successfully performed without complications. The patient was discharged without any sequelae ten days later. The pathology report indicated the diagnosis of extra-adrenal pheochromocytoma.

Unexpected pheochromocytoma may lead to a fatal hypertensive crisis during surgery. For anesthesiologists and surgeons who encounter an unexpected hypertensive crisis during surgery, undiagnosed pheochromocytoma should always be considered.

Introduction

Extra-adrenal pheochromocytomas (PHEOs) of the neural crest-derived sympathetic ganglia are known as paragangliomas (PGLs) and account for 15% of all PHEOs1,2. PGLs are more likely to be malignant (29-40%) than adrenal PHEOs (10-15%)1,2. Extra adrenal PHEOs or catecholamine-secreting PGLs develop in the paraganglion chromaffin cells of the sympathetic nervous system. Subsequently, they are widely distributed near or within the autonomic nervous system and therefore they can be found anywhere in the sympathetic ganglia along the sympathetic chain from the base of the skull and neck to the pelvis, prostate gland and bladder3-5.

Most extra-adrenal PGLs are histologically benign but some can synthesize, store, and secrete catecholamines from the tumor. The presence of synchronous metastases is rare at initial diagnosis (approximately 10% for PHEOs and 34% for PGLs), but can occur even 20 years after diagnosis with the most common metastatic sites being the local lymph nodes, bone (50%), liver (50%) and lung (30%)6. Recently, specific genes related to PHEOs/PGLs pathogenesis were found to confer...
an increased malignancy risk\(^7\).

Sometimes, extra-adrenal PHEO’s can be discovered during procedures or interventions that provoke release of catecholamines from the tumor. In such situations, endocrine emergency can occur with an unpredictable course and hemodynamic instability during surgery, especially in patients who have not been appropriately prepared for surgery\(^8\)–\(^10\).

PHEOs/PGLs of the spine will seldom be considered in a presurgical differential diagnosis due to its rarity (17%) and nonspecific imaging features\(^11,12\). Only 14 thoracic spinal PGLs have been reported, and spinal cord compression was the presenting feature in every case. Three of those cases involved metastases and two were functional\(^11,12\).

We report a case of a patient with a past surgical history of laparoscopic excision of PHEO ten years ago, who presented with a thoracic paravertebral tumour causing spinal nerve root compression and lower limbs neurologic symptoms.

**Case report**

A 52-year old female (77kg, 164cm), ASA II, presented to the hospital with thoracic back pain and lower limb weakness. She had a history of type 2 diabetes mellitus treated with oral hypoglycemic agents, and a past surgical history of laparoscopic excision of pheochromocytoma ten years ago. However, after the adrenalectomy procedure the patient was normotensive. At admission the blood pressure (BP) was 132/78 mmHg and the pulse rate 76 beats/min.

MRI confirmed the presence of a large, not well-demarcated tumour in the left paraspinal region of the T1–T4 vertebrae (Fig.1) Findings were suggestive of a narrow infiltrative process with an extraosseous soft tissue component extending through the neural foramina and epidural space compressing the spinal cord at T1 and T3 levels, causing cord compression at T3 level. The patient was initially diagnosed to have thoracic paravertebral tumor (neuroendocrine carcinoid tumour) with spinal nerve root compression and was scheduled for thoracic decompression laminectomy and instrumentation.

On the morning of surgery the patient was premedicated with diazepam 5 mg orally. In the operating room standard monitoring was applied, with electrocardiogram (ECG), pulse oximetry, and noninvasive blood pressure (BP) before the induction of anesthesia. Anesthesia was induced intravenously with propofol 160 mg, fentanyl
100 mcg, and rocuronium 60mg. After tracheal intubation, additional monitoring included central venous pressure and continuous arterial pressure measurement. Electrodes for neurophysiologic monitoring of somatosensory evoked potential and motor evoked potentials were applied and the patient was positioned in prone position with pressure points secured. The patient remained hemodynamically stable during induction, intubation, and surgical incision. Sevoflurane was discontinued for better neurophysiology monitoring, but sometimes it was used, after informing the neurophysiologist. Propofol infusion 100 mcg/kg/min and remifentanil infusion 0.06 μg/kg/min on 50% air-oxygen mixture were used for maintenance of anesthesia.

During intraoperative manipulation of the tumor, there was a sudden surge of blood pressure to 250/125 mmHg with tachycardia 140 beats/minute. The ECG showed supraventricular arrhythmia and T-wave inversion. Therefore an extra-adrenal pheochromocytoma was suspected. Initially this was managed by stepping up the dose of propofol and remifentanil infusions, increasing the depth of anesthesia. The surgeon was asked to stop immediately the tumor manipulation in order to prepare additional medication. During surgical manipulations anesthesia was further deepened by increasing propofol from 100 to 250mcg/kg/min and remifentanil from 0.6 to 3.0 mcg/kg/min, respectively. The value of BIS decreased from 40-50 to 25. However, the BP continued to be high (190/110 mmHg). Nitroglycerine infusion was started at 5mcg/min and titrated up to 20 mcq/min, and labetalol intravenous boluses (a combined α- and β-adrenergic blockade) were administered (20 mg of labetalol in four doses of 5 mg each) to control the heart rate. Additionally, hydralazine intravenous boluses were administered (50 mg in ten doses of 5 mg each). Due to surgical technical reasons the tumor was not totally removed since it was attached to the spinal cord. After surgery the patient was taken intubated and ventilated to the intensive care unit with low dose nitroglycerine infusion. The patient was discharged home 10 days later. The pathology report confirmed the diagnosis of metastatic pheochromocytoma.

Discussion

The perioperative course and anesthetic management of patients with undiagnosed catecholamine-secreting PHEOs or PGLs has typically been reported only in small case series. The true incidence of unsuspected intraoperative catecholamine producing neuroendocrine tumors remains unknown. Although considered rare tumors with a prevalence of 0.1-0.5% in the general population, they are diagnosed in only half of the patients on whom a pheochromocytoma is found on autopsy.

Extra-adrenal PHEOs exhibit a highly variable clinical presentation depending on their secretory profile with 88% of cases presenting with headaches, sweating, palpitations, and paroxysmal or sustained hypertension. Hypertension is constant in 50% of patients, paroxysmal in 30% and absent in 20%. However, in the absence of typical hypertension or for its rarity and nonspecific signs and symptoms, and diagnosis may be delayed or overlooked. Instead, most patients presented with mass effect related symptoms or incidentally from imaging studies such as a CT or MRI for other clinical conditions. Only 20% of extra-adrenal paragangliomas have been discovered due to hyper-functioning tumors.

Interestingly, in our case the patient was normotensive, after the past surgical laparoscopic excision of PHEO ten years ago, and presented with a thoracic paravertebral tumour causing spinal nerve root compression and lower limbs neurologic symptoms. Additionally, the patient remained hemodynamically stable during induction, laryngoscopy and surgical incision. An undiagnosed extradrenal PHEO was highly suspected based on the hypertensive crisis caused by tumor manipulation during the surgery. This is only the 4th documented case and only the third to present functional adrenergic symptoms.

Intraoperative manipulation of such tumors likely causes increased levels of catecholamine release and dramatic or even catastrophic hemodynamic changes. Historically they have been associated with a mortality rate of up to 40%, while others increase the mortality rate close to 80%. However, recent literature using the collective experience extracted from case reports and case series of
incidental catecholamine producing neuroendocrine tumors, suggests a lower than historically reported perioperative mortality to 8%\(^9\). Improved monitoring, better availability of intravenous antihypertensives, and advances in anesthesiology may partially explain this finding\(^9\). The diagnosis of pheochromocytoma was suspected intraoperatively only in 26% of patients\(^9\).

A higher index of suspicion intraoperatively may improve outcomes for patients with such tumors by promoting earlier and more aggressive hemodynamic management. Cooperation with the surgical team is important. Like in our case the surgeon should be asked to stop immediately the tumor manipulation in order to stop the trigger of catecholamine release and give time to anesthetist to prepare additional medication. Multimodal antihypertensive therapy including the use of an alpha adrenergic blocker or a combination antihypertensive medication containing an alpha receptor blocking component should be given early for the treatment of unexplained perioperative hypertensive crisis. The majority of the cases report nitrates as the intraoperative antihypertensives used, followed by beta-blockers and limited use of some form of alpha receptor blockade (33%)\(^9,10\).

We controlled hypertensive responses with deepening of anesthesia and analgesia levels like in other cases\(^19,20\). Especially, the use of high dose remifentanil infusion (\(>2\)mcg/kg/min) has been proved a safe and effective temporary treatment and may give the necessary time for preparing advanced antihypertensive medications\(^20\). The use of long-acting vasoactive medications compared to short-acting may exacerbate the hemodynamic instability\(^8,10\). When wide and perceptuous swing in the BP and heart rate, more short-acting vasoactive drugs rather than long-acting drugs are preferred and recommended\(^8,10\).

Based on the current evidence, it is very common for the patient to present persistent hypotension after tumor removal\(^11,5,8,12,19,20\). This may be ascribed to abrupt fall in catecholamine which leaded to a sudden dilation of the vasculature, leading in profound hypotension. However, in our case this did not occur and instead the patient needed low dose nitroglycerine infusion (1-5 mcg/min). This may attributed to the fact that the functional tumor was not totally removed. Therefore, there was a small part of the tumor still secreting catecholamines at a lower concentrations.

Although malignancy rate of these tumors are approximately 10%, their overall 5-year survival rate is less than 60%\(^6,21\). Malignant PHEO usually has poor prognosis. Malignant PGLs can also be treated surgically, but the prognosis depends primarily on whether the tumour metastasises. Spinal metastatic PHEOs/PGLs have led to pathologic fractures and spinal cord compression. The best combination of therapy for metastatic spinal PHEOs/PGLs appears to be surgical decompression followed by chemotherapy, molecular targeted therapy and radionuclide therapy with either 131I-MIBG or radiolabelled somatostatin analogues\(^22\).

In conclusion, unexpected pheochromocytoma causes increased levels of catecholamine release and may lead to dramatic or even catastrophic hemodynamic changes during surgery. A higher index of suspicion intraoperatively may improve outcomes for patients with such tumors by promoting earlier and more aggressive hemodynamic management. For anesthesiologists and surgeons who encounter an unexpected severe hypertensive crisis during surgery, undiagnosed pheochromocytoma should always be considered.
References

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**Side effects**

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**Precautions**

- Hypersensitivity to sugammadex or to any component of the formulation
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**References**

1. BRIDION Summary of Product Characteristics (SPC)

**Summary**

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