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Case Report

How to avoid intraoperative complications of active paragangliomas?

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ABSTRACT

Background: Paragangliomas (PGs) are very rare neuroendocrine tumors that can be found in unusual locations such as the spinal canal. Some PGs may be endocrinologically active, containing neurotransmitters such as noradrenaline, adrenaline, and serotonin. This can lead to unexpected neurotransmitter release during the removal of PGs, leading to a hypertensive crisis.

Case Description: We present two patients who underwent surgical removal of a secretory filum terminale PG.

Conclusion: If laboratory tests are suggestive of a secretory tumor, surgery should include anesthesiologic preparation similar to cases of pheochromocytoma.

Keywords: Neuroendocrine tumors, Paraganglioma, Surgery, Complications, Pre-operative Screening

INTRODUCTION

Paragangliomas (PGs) are rare neuroendocrine tumors mostly found in the carotid body, thoracoabdominal sympathetic nerves, and glomus jugulare. Still, they may also occur in other unusual sites, such as the spinal canal.[7] Given their histology and their slow growth, they are classified as grade I tumors by the World Health Organization.[6] Nonetheless, they have the potential to metastasize; therefore, they should not be considered benign.[9] Spinal cord and cauda equina PGs can present with low back pain, sciatica, hypoesthesia, sphincter dysfunction, and paraparesis.[10] While PGs are diagnosed based on histopathological findings, differentiating PGs from other tumors (e.g., myxopapillary ependymomas, meningiomas, metastases, and nerve sheath tumors) on imaging grounds (magnetic resonance imaging [MRI]) can prove challenging.[6] When there is clinical suspicion of PGs, digital subtraction angiography may be helpful in identifying their well-defined vascular pattern and should be considered in preparation for surgical excision.[6] Treatment of PG involves total excision, while the role of adjuvant radiotherapy and chemotherapy is still controversial.[10] In some cases, PGs may also be endocrinologically

functional, and indeed, some studies found substantial concentrations of neurotransmitters such as noradrenaline, adrenaline, and serotonin in these tumors. Not recognizing active PGs can have serious intraoperative consequences. We present and discuss two patients who underwent surgical removal of highly suggestive, filum terminale, and endocrinologically active PGs.

CASE 1

A 48-year-old male patient presented with back pain lasting two years, radiating into both lower extremities. Associated symptoms were severe episodes of anxiety and tachycardia, to which, initially, not sufficient attention was given. Lumbar spine MRI showed a contrast-enhancing intradural lesion occupying the spinal canal at L2 on T1-weighted MRI [Figure 1a]. Intraoperatively, the lesion was well encapsulated with a solid capsule [Figure 1b]. As the lesion was localized anteriorly, to respect the nerve roots, minimal coagulation was necessary to reduce the tumor's dimensions. In this phase, the blood pressure (BP) spiked slightly (150/110 mmHg). Finally, the lesion was mobilized, and its cranial and caudal adhesions to the filum terminale were coagulated and cut. The 1st days after intervention were uneventful. A lumbosacral MRI (day six post-surgery) confirmed total tumor removal and excluded complications. The patient was transferred to rehabilitation with progressive improvement of ambulation. Histopathology showed an endocrinologically active PG.

CASE 2

A 48-year-old male patient presented to our department for chronic low back pain. The patient had also been referred separately for evaluation of panic attacks and an anxiety disorder in the previous two years. A lumbosacral MRI showed an intradural lesion behind the L3 vertebral body, which showed homogeneous enhancement [Figures 2a and b]. The patient underwent total surgical excision of the lesion. The surgical procedure was uneventful. The histological analyses were compatible with spinal PG. A postsurgical MRI showed a total removal of the lesion without complications. At one year follow-up, he is pain-free and did not suffer from any panic attacks or an anxiety disorder since the surgery.

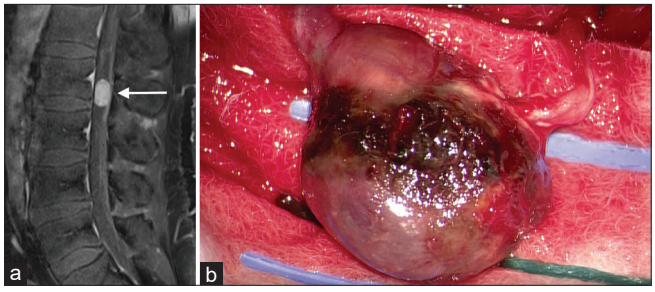

Figure 1: (a) A sagittal contrast-enhanced T1-weighted MRI image showing a homogenous contrast-enhancing lesion (as indicated by arrow). (b) Intraoperative image of tumor.

HISTOPATHOLOGICAL ANALYSIS

Patient 1

The specimen was a two × 1.2 × 1 cm encapsulated brown nodule with a homogeneous appearance. Microscopically, the lesion had sharp borders, and it was surrounded by fibrous tissue with focal intra- and peri-capsular calcifications. The nodule consisted of a benign neoplastic proliferation of cells with round/oval nuclei and finely dispersed chromatin; tumor cells were arranged in lobules and nests with an extensive intervening capillary network [Figure 3], and they focally formed perivascular structures resulting in an ependymoma-like pattern.

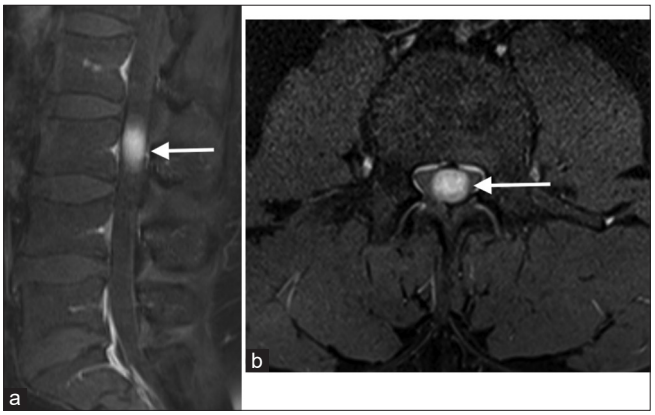

Figure 2: A sagittal (a) and axial (b) contrast-enhanced MRI image showing a homogenous contrast-enhancing lesion (as indicated by arrow).

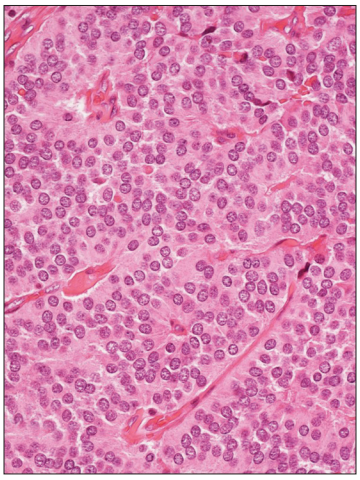

Figure 3: Image of tumor specimen hematoxylin and eosin (H&E) stained characterized by rich vascularity and with lobular growth pattern (×40).

Then, a few vessels showed hyaline walls, and others were congested; necrosis, vascular, and capsular invasion were not identified.

Neoplastic cells were immunoreactive for synaptophysin and chromogranin-A, confirming their neuroendocrine differentiation [Figure 4] and for cytokeratin (anti-Pan Keratin AE1/AE3/PCK26, Ventana). The proliferation index was about 5%.

Patient 2

Intraoperatively, the lesion appeared gray and was of a hard consistency.

Grossly, the specimen was a 1.7 cm encapsulated oval and brown nodular mass.

Histopathological examination showed a well-circumscribed nodule composed of nests of monomorphic round cells and a prominent thin vascular network with congested vessels. Capsular invasion and necrosis were not observed [Figure 5].

Immunohistochemical studies were performed, and tumor cells were positive for chromogranin [Figure 6a], they preserved Succinate Dehydrogenase B (SDHB) cytoplasmic granular expression [Figure 6b], and the Ki67 value was about 2% [Figure 6c].

DISCUSSION

Spinal PGs are rare, with an incidence in the general population of circa 0.07/100,000 inhabitants.

Shtaya *et al*.[11] reported in their recent and excellent review on PGs that circa 200 cases have been reported so far in the English literature. The mean age of the patients was 48.8 ± 1.2 years. The location of tumors was mainly in the lumbar L1 level or below, while one case was reported in the thoracic spine at T3. Lower back pain with radiculopathy was the most reported symptom in 94% of cases, while bowel and bladder disturbances were only in 22 and 15% of cases, respectively. As symptoms of paragangliomas are mostly non-specific the diagnosis is often delayed for years.[12]

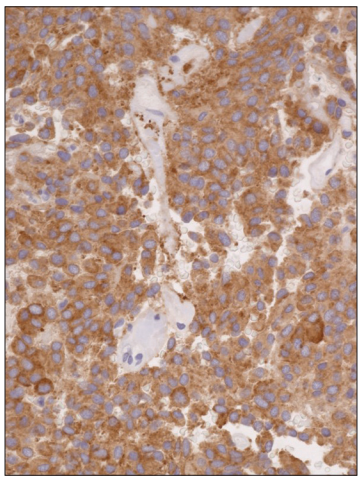

Figure 4: Tumor cells are diffusely and strongly immunoreactive for synaptophysin (× 40).

Diagnosis for intradural lesions is based on MRI. As imaging findings are non-specific,[12] a wide range of other space-occupying lesions need to be taken into consideration for differential diagnosis, such as ependymoma, meningioma, single metastasis, or schwannoma. On MRI-T1-weighted images, PGs appear isointense to the spinal cord, while hyperintense on T2-weighted images shows contrast enhancement with gadolinium. Only a biopsy confirms the diagnosis.

On an endocrinological basis, PGs are classified as secretory and non-secretory neoplasia's. There have been a few documented cases in the literature of PG symptomatology marked by sympathetic hyperactivity, such as paroxysmal hypertension and metabolic disorders.[5] Some reports indicate that subclinical PGs may secrete excess catecholamines.

The major concern of PGs is that they can cause lethal hypertensive crises through excessive catecholamine-release. Symptoms can vary and be unspecific, such as visual disturbances, increased heart rate, headache, and vomiting. Therefore, a high degree of suspicion is critical for prompt diagnosis and management. Of primary concern is BP control, for example, through bolus administration or continuous infusion of vasodilators such as urapidil, labetalol, or nitroglycerine. Other options are the application of phentolamine, a long-acting, adrenergic, and alpha-receptor blocking agent given as an intravenous bolus of 2.5–5 mg at the rate of 1 mg/min and which can be repeated every 3–5 min. To reduce the risk of an intraoperative hypertensive crisis, proper preoperative management focusing on BP adjustment and sufficient blood volume to assure a hemodynamic stable patient is paramount. Preparation of patients, especially for catecholamine-producing tumors and cardiovascular assessment, is a cornerstone of this surgery. The objective of the preparation is to limit preoperative hypertension to 160/90 mmHg and the vasoconstrictive, tachycardic effects of catecholamine. The tumor's size (>4 cm), the level of catecholamines secreted, a mean preoperative pressure >100 mmHg, and hypovolemia are factors leading to cardiovascular instability.

If manipulated during surgical excision, they could theoretically release neurotransmitters and provoke sudden abnormal BP variations and complications such as cerebrovascular accidents or pulmonary edema.[4] An intraoperative hypertensive crisis requires clipping the tumor pedicle.

From a histopathological point of view, these tumors may also show an uncommon immunohistochemical profile concerning cytokeratin expression; in our case, tumor cells were positive for this epithelial marker.

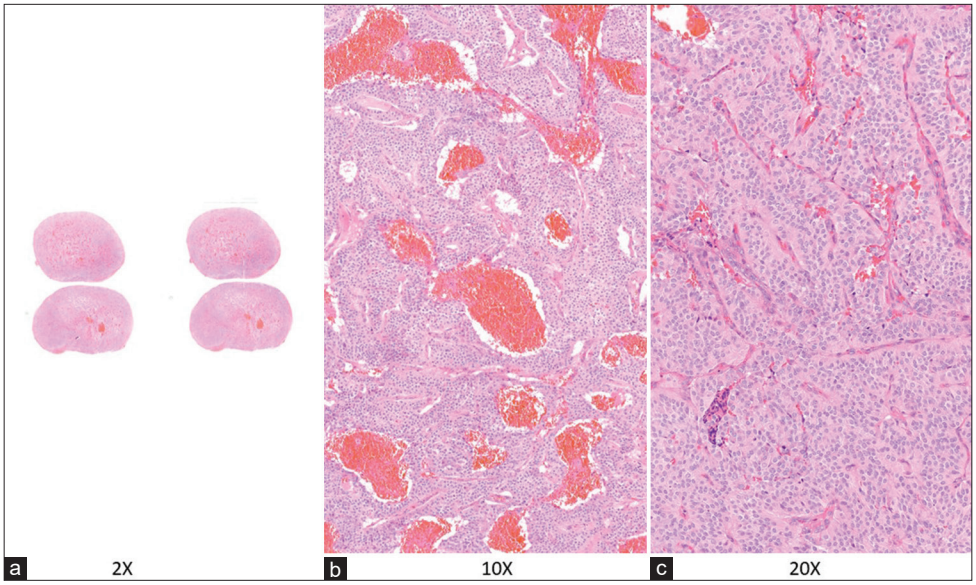

Figure 5: (a-c) Formalin-fixed paraffin-embedded tissue sections hematoxylin and eosin (H&E) stained (a: ×2 magnification, b: ×10, c: ×20) (a) showing a well-circumscribed nodule. (b and c) A tumor is composed of nests of round cells and a prominent vascular network.

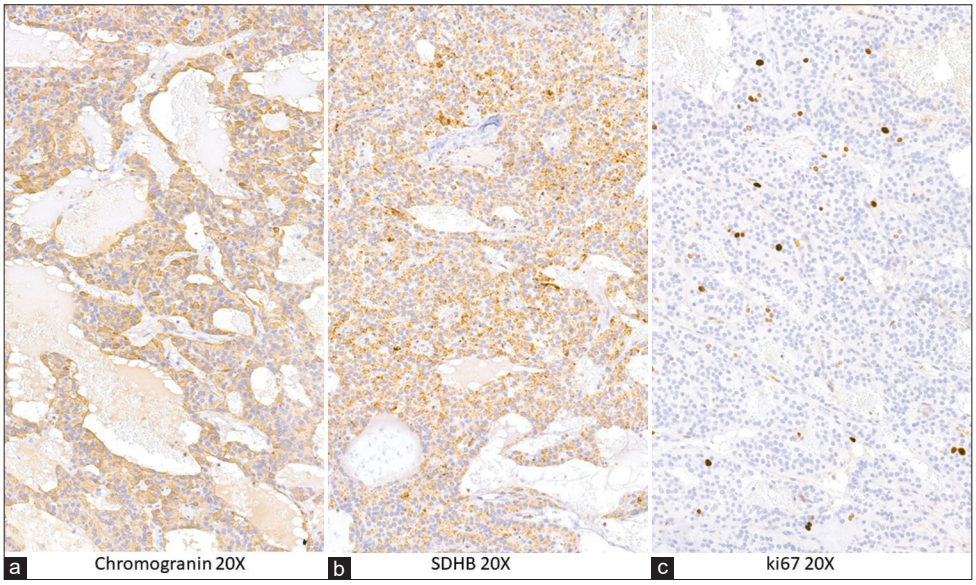

Figure 6: (a-c) Tumor cells are immunoreactive for (a) chromogranin, (b) and they preserved SDHB cytoplasmic granular expression, and (c) Ki67 value is about 2%.

It is well known that most PGs are not immunoreactive for cytokeratin, a feature allowing differentiation from other neuroendocrine neoplasms; positive cytokeratin staining is a rare occurrence, as supported by Dermawan *et al*.[2] Despite this, a few cases of extra-adrenal PGs, including at the cauda equina, have been described to be reactive for cytokeratin[1], even with an intense and diffuse staining pattern.[8]

Given the possibility of neurosecretion, subtle endocrine symptoms have to be considered when PGs are suspected. During capsule coagulation, we noted a slight peak of BP, very likely the consequence of catecholamine release by the tumor. We achieved a total removal without the need for debulking.

CONCLUSION

When suspecting PGs, the biochemical work-up should include the determination of free metanephrine or urinary metanephrine, urinary adrenaline, and noradrenaline. Furthermore, 24 h BP monitoring should be considered. If

laboratory tests are suggestive of a secretory tumor, surgery should include an anesthesiologic preparation similar to cases of pheochromocytoma.[4]

Take-home points

- PGs are very rare types of neuroendocrine tumors
- PGs may be endocrinologically active, containing neurotransmitters
- Preoperative preparation should focus on adequate BP adjustment and blood volume status aiming at a hemodynamically stable patient
- The risk of not recognizing active PGs can have serious intraoperative consequences.

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Data availability statement

All data related to these two cases are mentioned in the manuscript and can also be requested directly by the corresponding author, Dr. Zekaj.

Ethical approval

Not applicable.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest

There are no conflicts of interest

Use of artificial intelligence (AI)-assisted technology for manuscript preparation

The authors confirm that there was no use of artificial intelligence (AI)-assisted technology for assisting in the writing or editing of the manuscript and no images were manipulated using AI.

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