Received: 15 December 2023 | Revised: 10 February 2024 | Accepted: 20 February 2024

DOI: 10.1002/ccr3.8584

CASE REPORT

Clinical Case Reports Open Access WILEY

Paraganglioma at the cerebellopontine angle: A case report and review of literature

Nadeem Akhtar[1] | **Fatimah Shahid**[2] | **Alishba Shezal Ali**[2] | **Qurat Ul Ain Muhammad**[2] | **Noor Mahal Azam**[2] | **Bishal Dhakal**[3] | **Muhammad Ibrahim**[2] | **Nehal Nadeem**[4]

[1]Department of Neurosurgery, Rawalpindi Teaching Hospital, Punjab, Pakistan

[2]Department of Neurosurgery, Rawalpindi Medical University, Punjab, Pakistan

[3]Department of Neurology, Nepalese Army Institute of Health Sciences, Kathmandu, Nepal

[4]Department of Internal Medicine, Shifa College of Medicine, Islamabad, Pakistan

Correspondence
Bishal Dhakal, Nepalese Army Institute of Health and Sciences, Kathmandu 44600, Nepal.
Email: swarnimdhakal@gmail.com

Key Clinical Message

Paragangliomas (PGLs) are rare neuroendocrine tumors. Sometimes, these tumors secrete excessive catecholamines, which results in the manifestations of various signs and symptoms, usually with a triad of hypertension, tachycardia, and headache. We report the case of a 42-year-old woman presenting with uncontrolled hypertension, right facial palsy, vomiting, and disturbed gait. Diagnosis for PGL was confirmed on postoperative histological examination of the excised mass and correlated with preoperative clinical and radiological findings. Tumor excision was done via a suboccipital craniotomy approach. Our case presents the typically severe features of a jugulotympanic PGL, but most importantly, it highlights the necessity of biochemical diagnosing, thorough probing of the causes of hypertension, and a multi-disciplinary approach in dealing with these tumors. Moreover, the case emphasizes necessitating the use of preoperative embolization in vascular tumors of the head and neck to avoid a hemorrhagic crisis during surgery. Unfortunately, due to a lack of adequate hospital funds, the surgeon had to proceed without preoperative embolization. Despite such a risk, the excision was a success.

KEYWORDS

catecholamine secreting tumor, cerebellopontine angle, extra-adrenal paraganglioma, head and neck neoplasms, hypertension, hypoxia-inducible factor (HIF)-1α

1 | INTRODUCTION

Paragangliomas are neuroendocrine tumors arising from sympathetic or parasympathetic ganglia and present in different body sites, specifically around the carotid body, abdomen, pelvis, head, and neck.[1] PGLs represent 0.6% of all head and neck neoplasms.[2]

These tumors affect 0.7 to 1 per 100,000 person-years in the US[3] and PGLs at the cerebellopontine angle (CPA) are even rarer. Most PGLs are benign, but some can metastasize. Computerized tomography (CT) scans of the lungs, liver, and bones or DOTATATE PET are essential to rule out metastasis.[3] The chances of spread increase for poorly differentiated tumors detected at later stages, which is often the case.

The prognosis depends on the time of detection, local invasion, metastasis, available treatment, and genetic predisposition. It varies between a normal life expectancy and a 5-year survival rate of 11.8%[2] PGLs and pheochromocytomas exhibit the highest degree of heritability among human neoplasms.[4] PGLs are linked to mutations in the succinate dehydrogenase (SDH) gene; loss of both alleles produces a pseudo-hypoxic state favoring PGL development.[5,6] Moreover, hypoxia promotes the augmentation of metastasis and the spread of chaotic neovascularization by activating hypoxia-inducible factor (HIF).[5] We report the rare case of a woman diagnosed with a jugulotympanic PGL.

2 | CASE PRESENTATION

2.1 | Case history

Patient was 42-year-old female, living at a high altitude area, which is associated with increased incidence of PGLs. She presented in the neurology outpatient department (OPD) with complaints of right-sided deviation of the angle of the mouth, vomiting, vertigo, and disturbed gait for 6 months. She was diagnosed with hypertension 2 years ago and was on calcium channel blockers; however, her blood pressure remained uncontrolled. Family members noted drooping of the right side of the mouth 6 months back; it progressed to drooling and difficulty chewing. She also complained of excessive watering and difficulty closing her right eye. Excessive vomiting started 2 weeks prior to presentation at hospital. There were one to two projectile episodes of vomiting occurring daily and no hematemesis, abdominal pain, diarrhea, fever, or neck rigidity. Gait disturbances led to increased falls at home.

On examination, the patient was conscious, well-oriented, and vitally stable. House–Brackmann Grade IV right facial nerve palsy was observed. The right pupil was nonreactive, while the left pupil was sluggish reactive due to mass effect of the tumor and raised intracranial pressure. Reflexes in the upper and lower limbs were intact with bilaterally down-going plantars. The tone was normal, and the power was five, according to the Medical Research Council (MRC) scale. Power for both upper and lower limbs was 5/5, bilaterally. The sensory system was intact.

2.2 | Radiological investigations

Pre- and post-contrast magnetic resonance imaging (MRI) of the brain revealed an ill-defined, lobulated, extra-axial lesion at the right CPA. It measured 71 × 54 × 54 mm. The lesion appeared isointense on T1 and hyperintense on T2 and fluid-attenuated inversion recovery images. There was intense post-contrast enhancement with a "salt and pepper" appearance as shown in Figure 1. The lesion extended from the CPA along the internal jugular vein and internal carotid artery as shown in Figure 2. Right trigeminal and facial nerves were involved. It had pushed the brainstem to the contralateral side and effaced the fourth ventricle.

2.3 | Treatment plan

The patient and her spouse were counseled regarding her condition. High-risk informed consent was taken before surgery. For hydrocephalus, an endoscopic third ventriculostomy was performed. However, while awaiting surgery she developed sudden bilateral painless loss of vision and right-sided cerebrospinal fluid (CSF) otorrhea. Blood pressure was controlled with losartan potassium 25 mg.

An internal debulking surgery was performed under general anesthesia. With the patient in the left lateral position, a "Lazy S incision" was made, followed by a dissection of the underlying muscles. After suboccipital craniotomy posterior to the mastoid, the dura was opened with a medial C-shaped incision along the inferior edge of the transverse sinus and the posterior edge of the sigmoid sinus. The incision was kept 3–5 mm away from them. Subsequently, medial cerebellar retraction revealed an aggressive-looking, but well-encapsulated tumor. When incised the tumor bled profusely. It was controlled with electrocauterization and ligation. Consequently, the blood pressure dropped to 50/0 mmHg. Along with aggressive

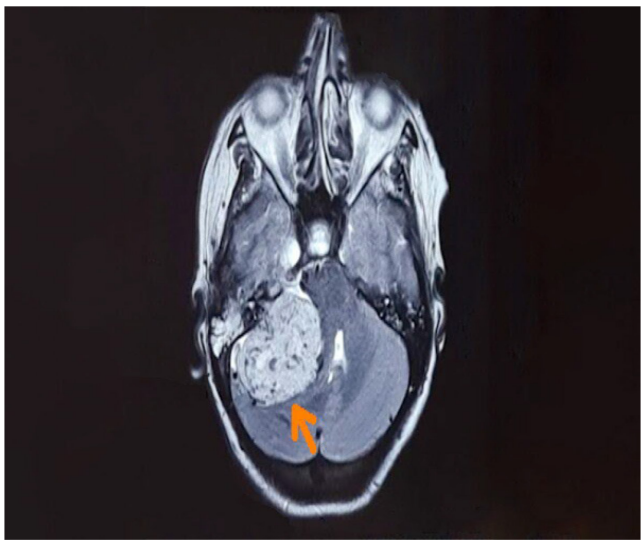

FIGURE 1 Pre-operative contrast-enhanced magnetic resonance imaging (MRI) brain (axial section). Arrow pointing toward a well-demarcated tumorous mass at right cerebellopontine angle (CPA) with typical salt and pepper appearance.

fluid replacement 3 units of red cell concentrate were transfused. Once the bleeding and the blood pressure were controlled, the surgeon proceeded with tumor excision.

The tumor walled the petrous part of the temporal bone and extended into the jugular foramen. It had completely obliterated the VII, VIII, IX, X, and XI cranial nerves on the right side with an extracranial extension in the temporal region. After a lengthy procedure of 4 h, the dura was stitched back, and the layers were closed in reverse order. The postoperative non-contrast CT scan revealed successful excision of the tumor as shown in Figure 3.

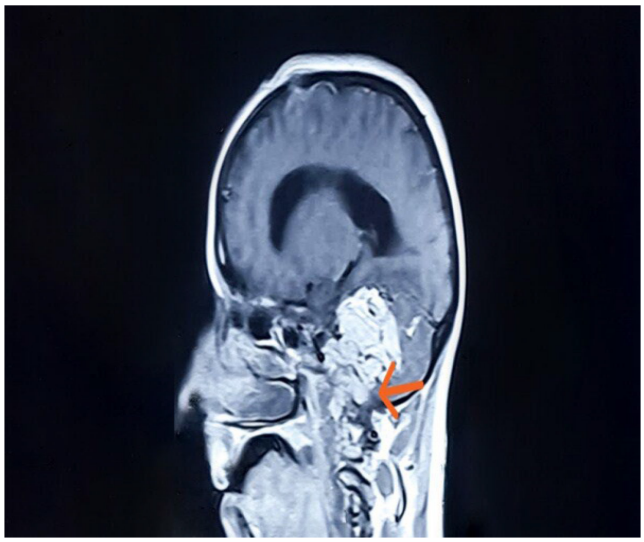

FIGURE 2 Pre-operative contrast-enhanced magnetic resonance imaging (MRI) brain (sagittal section). Arrow points to the tumor with intense post-contrast enhancement at the cerebellopontine angle (CPA). Its extension into the right parapharyngeal space and right internal auditory canal can also be seen.

2.4 | Histopathological examination

Histopathological examination of the excised specimen revealed a Zellballen pattern. Immunohistochemical analysis showed sustentacular cells staining positive for S100. Chromogranin and synaptophysin were also positive. It was negative for oligodendrocyte transcription factor 2, glial fibrillary acidic protein, and cytokeratin. The antigen Kiel 67 proliferation index was 1% to 2%.

2.5 | Follow-up and outcome

The patient remained at the hospital for 20 days. She was kept on synchronized intermittent mandatory ventilation (SIMV) that is a volume control mode of ventilator for 2 days. On the third postoperative day, a tracheostomy was done. On the 14th day, a left-sided ventriculoperitoneal shunt was placed. She was discharged once improvement in GCS and hemodynamic stability was achieved. Bimonthly follow-up for 3 months, chest physiotherapy, and postural changes were advised. Her Glasgow Coma Scale was 10/15 (E4VTM6) at 3-month follow-up.

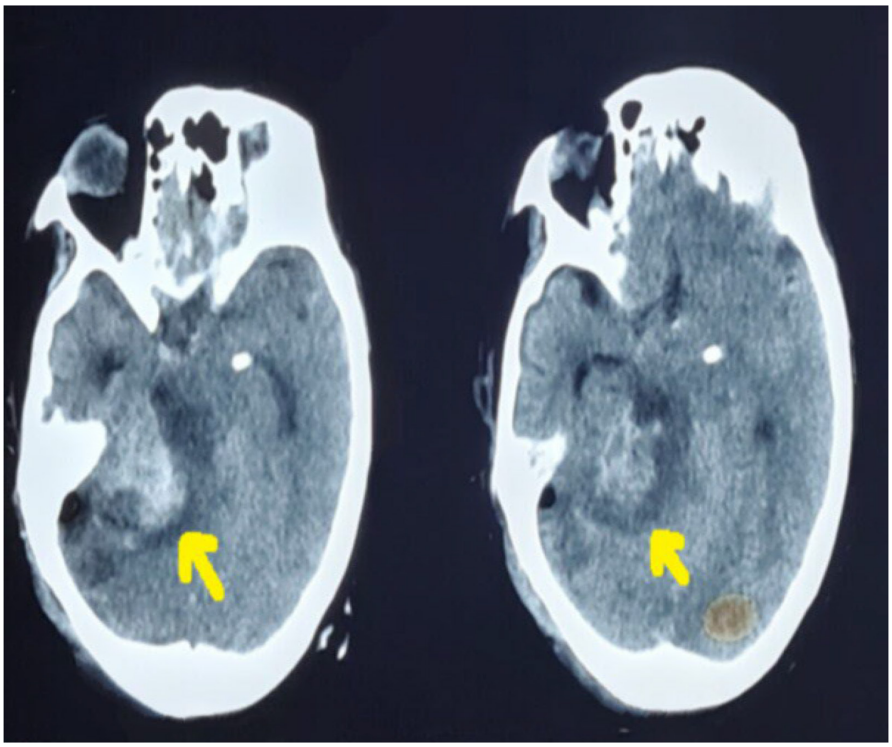

FIGURE 3 Post-operative non-contrast enhanced computerized tomography (CT)-brain (axial section). Arrows indicate successful tumor resection in the brain. Surgical intervention has removed the neoplastic lesion, indicated by the absence of abnormal tissue density. This scan confirmed the achievement of near-complete tumor excision.

3 | DISCUSSION

Our case involves a patient treated for jugulotympanic paraganglioma (jugulotympanic PGL). PGLs are categorized into adrenergic, noradrenergic, dopaminergic, and silent types based on catecholamine secretions.[6] Moreover, they are either sympathetic or parasympathetic. Latter are often non-secreting tumors.[1]

Presenting complaints depends upon the type of catecholamine secreted.[1,6] In our case, the patient was suffering from hypertension only for 2 years. She was prescribed calcium channel blockers, but the hypertension remained uncontrolled due to poor drug compliance. 37% of the Pakistani population suffers from primary hypertension.[7] Consequently, the physicians were not alarmed by the patient's significantly high blood pressure and therefore, did not probe further for any underlying etiologies.

PGL symptoms are called 'the great masquerades' due to their variable symptomatology, which subsequently contributes to a difficulty in establishing a timely diagnosis.[8] Hitherto, they are often underdiagnosed, leading to patient fatality.[1] The clinical presentation of PGLs can vary from tumors presenting with mass effects or exhibiting symptoms correlated with catecholamine hypersecretion to lesions discovered incidentally on radiological examination or screening for pathogenic variant carriers.[1] Secreting tumors characteristically present with hypertension, associated with a classic triad of headache, sweating, and tachycardia/palpitations.[1] The nature of these nonspecific clinical findings led to the formulation of a diagnostic workup for PGLs involving biochemical analysis supplemented with radiological imaging.[9] Measurement of 24-h urine catecholamines and metanephrines or fractionated plasma-free metanephrines is required for biochemical diagnosis.[9,10] This should be complemented by imaging studies either CT or MRI for tumor visualization.[9] In our case, the patient's condition deteriorated as she developed right-sided facial palsy, vomiting, vertigo, and disturbed gait. The sudden onset of the patient's symptoms and their increasing severity alerted the physicians of the possibility of a cranial pathology. A brain MRI scan demonstrated slight compression of the 4th ventricle, causing proximal hydrocephalus, explaining the patient's onset of episodes of vomiting. Additionally, displacement of the brainstem toward the left was observed, attributed to the tumor's mass effect. Consequently, it led to the development of vertigo and an unsteady gait in the patient. The predominant portion of the tumor was situated within the CPA, its extensions occluding the right cranial nerve VII. This led to the manifestation of right-sided facial paralysis. However, the patient's preoperative investigative procedures did not involve biochemical testing as physicians excluded the possibility of a PGL based on the initial clinical assessment. Furthermore, due to inadequate funds and a lack of appropriate facilities, a biochemical diagnosis could not be made for our patient. The diagnostic workup therefore relied on clinical examination and advanced imaging techniques, which suggested either a jugulotympanic PGL or vestibular/facial nerve schwannoma. Based on these the surgeon was more inclined toward the probability of it being a vestibular nerve schwannoma and went into the operation theater expecting to excise it. However, immense bleeding following an incision in the tumor's capsule and the aggressiveness of the tumor aroused the suspicion of a jugulotympanic PGL.

Following diagnostic workup, parameters such as the patient's age, associated comorbidities, previous treatment, tumor size and site, secretory activity, and potential for malignancy are considered before offering surgical extirpation, stereotactic radiosurgery, or stereotactic radiation therapy.[11] Complete eradication of head and neck PGLs was considered a Gordian knot due to the proximity of several important neurovascular anatomical structures, i.e., carotid artery, jugular vein, sympathetic chain, and the lower cranial nerves (IX–XII).[12]

The surgical approach for jugulotympanic PGLs is catered according to the Fisch and Mattox staging system.[1,13] When restricted to the middle ear cleft, the tumors are categorized into Class A, whereas those obliterating the ossicles with invasions into the hypotympanum fall into Class B. PGLs responsible for erosions of the carotid foramen, carotid canal, and the foramen lacerum belong to Class C, while tumors exhibiting intracranial extensions fall into Class D.[13] Class A and B tumors show promising outcomes with surgical resection, displaying excellent control and reduced cranial nerve damage postoperatively. However, radiotherapy is suggested as a more beneficial alternative for Class C and D tumors.[14] Preoperative embolization, approximately 24 to 48 h before surgery is recommended[15] to minimize blood losses and enhance surgical visualization for expedited tumor excision.[16] Due to financial constraints only, electrocoagulation was used to control intraoperative bleeding.

The jugular foramen can be accessed through various surgical approaches, depending upon the requirements of a particular case as well as the complexity of surrounding anatomical structures. Broadly, there are two approaches: anterolateral and posterolateral. The latter include retro sigmoid and far-lateral approaches.[17] Taking into account the tumor's location at the jugular foramen and its intracranial extension at the CPA, surgeons opted for a retro sigmoid approach with suboccipital craniotomy. Allowing access to the jugular foramen as well as the lateral part

of the brainstem, this chosen approach provided a clear surgical field for adequate tumor visualization. Moreover, the retro sigmoid approach with suboccipital craniotomy involves minimal brain manipulation and hence, reduces the risk of intraoperative complications.

Histopathological examination of the excised tumor revealed a characteristic Zellballen pattern[18] and immunohistochemical analysis served as standardized validation for the neuroendocrine tumor.[1] Genetically, PGLs can be sporadic and hereditary.[19] The Cancer Genome Atlas categorized patients of PGLs into three distinct disease clusters: pseudo-hypoxic, Wnt-signaling, and kinase-signaling.[1,19] The Wnt-signaling pathway regulates various developmental processes, such as cell proliferation and differentiation. In PGLs associated with the Wnt-altered subtype, there are mutations in the CSDE1 (cold shock domain containing E1) and MAML3 genes (mastermind-like transcriptional coactivator 3).[19] Both mutations contribute toward the abnormal cell proliferation and metastasis in PGLs. The kinase signaling cluster of PGLs includes those arising from mutations in the RET proto-oncogene, neurofibromin 1 (NF1) tumor suppressor, H-RAS and K-RAS proto-oncogenes, CSDE1, and ATRX.[19] All of these mutations lead to dysregulated cellular growth and proliferation in tumor cells.

The pseudo-hypoxic subtype is particularly important to our case; specifically, the genetic defects in the tricarboxylic acid cycle.[6] Most hereditary PGLs have been linked to genetic mutations of the genes encoding the SDH enzyme complex.[1] The SDH enzyme complex is an instrumental part of both the tricarboxylic acid cycle and the mitochondrial respiratory chain.[1] Additionally, the SDH genes are involved in tumor suppression.[1] Consequently, the succinate accumulation hypothesis postulates that SDH mutations lead to a buildup of excessive mitochondrial succinate, which enters the cytoplasm and inactivates α-ketoglutarate-dependent dioxygenases; this leads to the subsequent stabilization of HIFα. Evidence shows that the incidence of PGL is greater among populations residing at high altitudes due to exposure to chronic hypoxia.[20] Under conditions of normoxia, HIFs undergo hydroxylation by prolyl hydroxylases, a type of dioxygenase enzyme, which subsequently leads to ubiquitin-mediated proteasomal degradations of HIFs. However, in a state of hypoxia, this reaction is affected, with the reaction rate decreased and HIFs stabilized. Accordingly, it has been proposed that the loss of SDH causing succinate accumulation drives a pseudo-hypoxic state, playing a part in tumorogenesis.[20] Yet, further research is required to understand what role hypoxia plays in developing PGLs in those living at high altitudes. As our patient was a resident of a city located 7516 feet above sea level, there is good reason to suspect she might have harbored SDH gene mutations. Thus, a genetic workup distinguishes not only between sporadic and hereditary cases but also aids in tailoring treatment programs according to genetic sequencing.[18]

In conclusion, we present a rare case of a PGL located at the CPA, extending into the right cerebellar area and causing compression of the fourth ventricle. It highlights the importance of considering rare tumor types as potential diagnoses, even when patients present with seemingly innocuous symptoms such as uncontrolled hypertension. A thorough investigation of the patient's presenting complaint of hypertension could have facilitated with a timelier diagnosis of a PGL and consequently, yielded a better prognosis. Moreover, the inclusion of biochemical testing in the diagnostic workup could have alerted the physicians regarding the possibility of a PGL and aided in tailoring a better management and treatment plan. Finally, an accurate diagnosis of PGL necessitates a comprehensive approach involving clinical evaluation, radiological imaging, biochemical tests, and histopathological examination for definitive confirmation.

AUTHOR CONTRIBUTIONS

Nadeem Akhtar: Conceptualization; writing – review and editing. **Fatimah Shahid:** Investigation; resources. **Alishba Shezal Ali:** Resources; writing – original draft; writing – review and editing. **Qurat Ul Ain Muhammad:** Writing – original draft; writing – review and editing. **Noor Mahal Azam:** Resources; writing – review and editing. **Bishal Dhakal:** Data curation; resources; validation; writing – review and editing. **Muhammad Ibrahim:** Writing – review and editing. **Nehal Nadeem:** Writing – review and editing.

ACKNOWLEDGMENTS

We would like to extend our sincere appreciation to Dr. Qurrat Ul Ain Yousafi for her invaluable contributions, including assistance during the surgery, provision of pre- and post-operative notes, and patient monitoring which greatly enhanced the quality of this case report.

FUNDING INFORMATION

The study did not receive any grant from funding agencies in the public, commercial or not-for-profit sectors.

CONFLICT OF INTEREST STATEMENT

The authors report no conflict of interest.

DATA AVAILABILITY STATEMENT

No data was used.

ETHICS STATEMENT

This is a case report, therefore, it did not require ethical approval from ethics committee.

CONSENT

Written informed consent was obtained from the patient to publish this report in accordance with the journal's patient consent policy.

ORCID

Bishal Dhakal https://orcid.org/0000-0001-9432-5233

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How to cite this article: Akhtar N, Shahid F, Ali AS, et al. Paraganglioma at the cerebellopontine angle: A case report and review of literature. *Clin Case Rep*. 2024;12:e8584. doi:10.1002/ccr3.8584