CASE REPORT

Multiple Paragangliomas with Novel Mutation: A Rare Entity

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Abstract

Head and neck paragangliomas (HNPGLs) are rare, rarely functional tumors known to have a genetic predisposition. Carotid body tumors (CBT) are the most common HNPGLs followed by jugular bulb tumors, vagus nerve, and tympanic plexus. The prevertebral region is not the known area for these tumors as seen in our case making it a rare case. Mutations in SDH-D linked genes are commonly associated with multiple HNPGLs. SDH-D mutations with single-gene deletion are rare as seen in the present case. Bilateral carotid body tumors need to be managed in a staged manner. Patients with HNPGLs need annual clinical, hormonal, and radiological, surveillance for early diagnosis and management. First-degree relatives, especially males, need surveillance as SDH-D mutations exhibit maternal imprinting. We describe here the management of a middle-aged male who came with neck swelling on evaluation and was found to have nonfunctional bilateral carotid body tumors, mediastinal, and a rare prevertebral tiny lesion.

Keywords: Carotid body tumor, Novel mutation, Paraganglioma, Succinate dehydrogenase.

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Background

Paragangliomas are rare extra-adrenal tumors arising from paraganglia seen in relation to the sympathetic/parasympathetic chain in the head, neck, thorax, and abdomen.[1] Head and neck paragangliomas are slow-growing tumors (0.6%) and rarely secrete catecholamines (4–5%) hence nonfunctional.[2] These tumors occur near arteries and cranial nerves of branchial arches therefore close to carotid vessels and cranial nerves (X–XII). Most commonly arising from the carotid body, followed by the jugular bulb, vagus nerve, and tympanic plexus. The following section provides the description of a case of multiple paragangliomas presenting with bilateral carotid body tumors, prevertebral (rare), and mediastinal lesions with SDH-D novel genetic mutation.

Case Description

A gentleman aged 37 years came with complaints of painless, nonprogressive swelling on the right side of the neck for 20 years. Painful and gradually increased in size for last 2 years with no other complaints. He was not a known hypertensive. No similar complaints in the family members. On examination, his pulse was 80 beats/minute, and his blood pressure was 130/90 mm Hg.

On the right side of the neck, there was a 6 × 5 cm soft, nontender, smooth surface, pulsatile swelling located deep to sternocleidomastoid muscle at the level of thyroid cartilage (Fig. 1). There was no other palpable swelling. Systemic examination was normal. Ultrasound of the neck showed a hypoechoic lesion with cystic spaces arising in between internal and external carotid arteries confirming as CBT. Hormonal profile including 24 hours. Urine metanephrines and normetanephrines, PTH, TFT, and cortisol were normal. Because of the elevated blood pressure, α-blocker (prazosin) was started at the low dose of 5 mg/day and increased to 7.5 mg/day in a divided dose along with 4–5 liters of water intake and 5 mg of salt. β blocker (propranolol 20 mg twice daily) was started for tachycardia. Functional imaging by 68-Ga DOTANOC PET-CT showed multiple areas of increased

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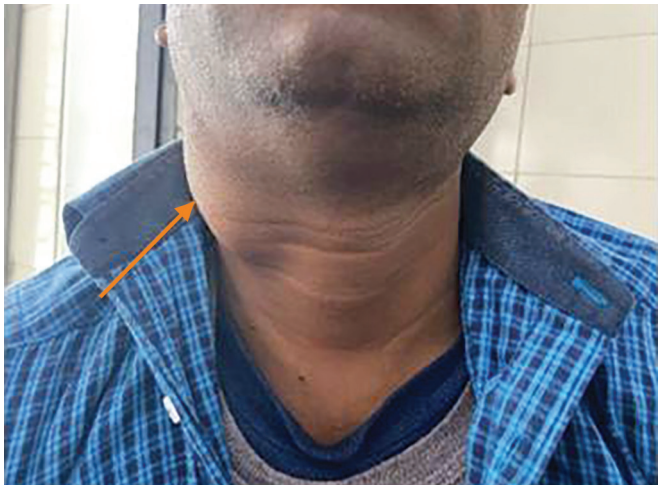

Fig. 1: Right side of the neck showing a 6 × 5 cm soft, nontender, pulsatile mass deep to sternocleidomastoid muscle

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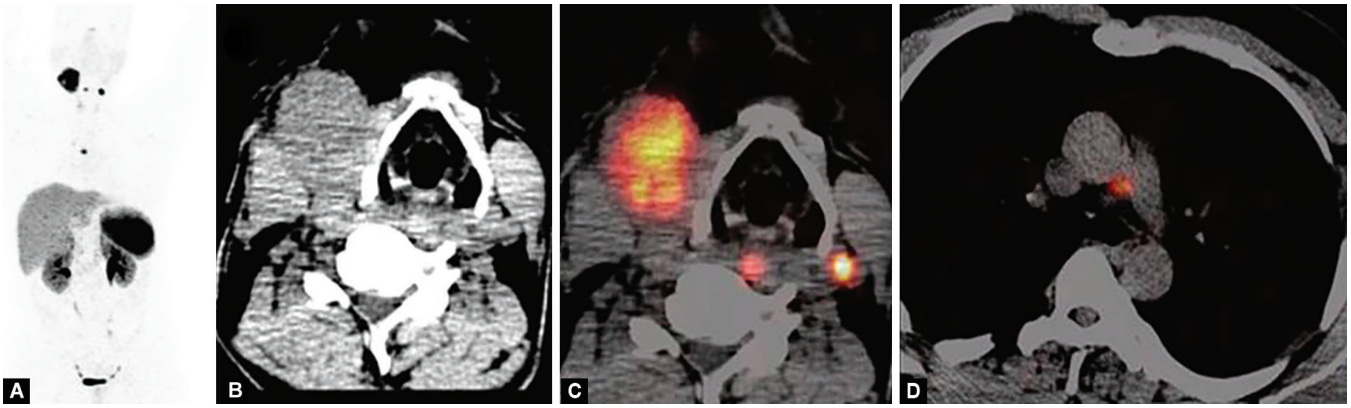
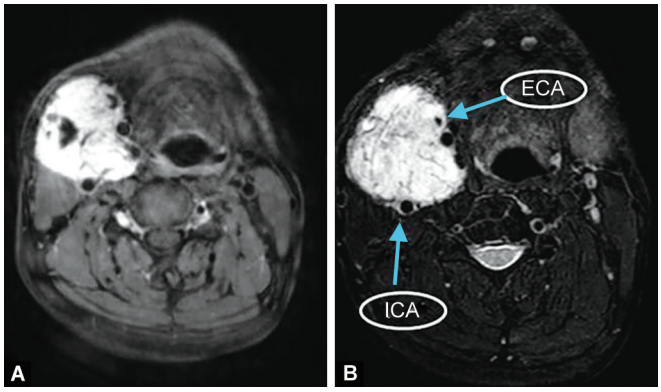


Figs 2A to D: (A) Maximum intensity projection image of 68-Ga DOTANOC PET-CT showing multiple areas of increased tracer uptake in the base of the skull; (B) Thoracic region corresponding to iso-hyperdense lesions in the bilateral cervical region prevertebral region; (C and D) Mediastinum on CT showing increased tracer uptake on fused PET-CT image



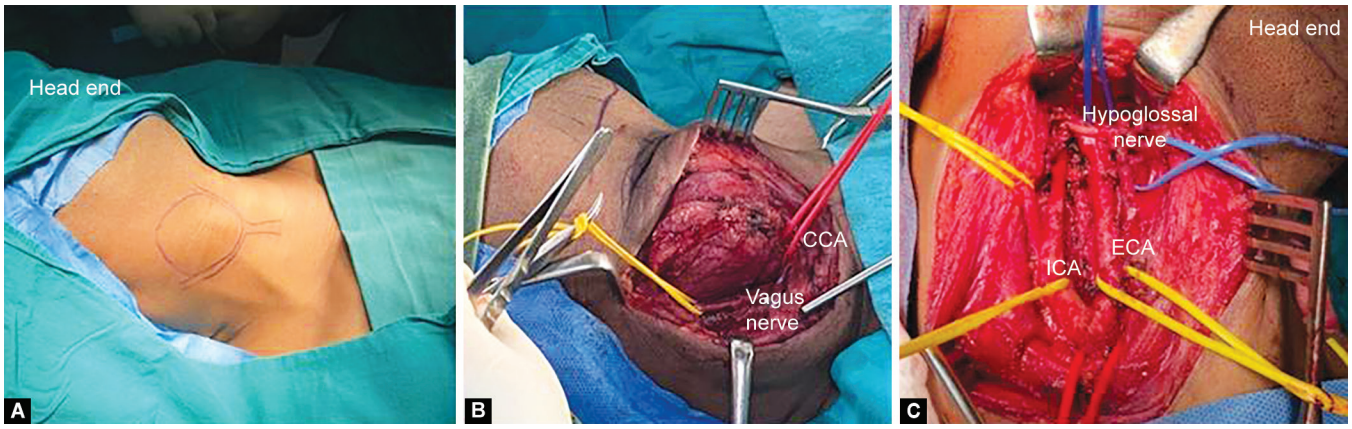
Figs 3A and B: MRI neck showing well-defined soft tissue mass measuring 53 × 44 × 49 mm (CCXTRXAP) in right carotid space (A) Showing iso-hyperintense on T1 images; (B) Showing T2-hyperintense lesion arising in between right carotid space splaying external carotid artery anteriorly and encasing it more than 2,700 and internal carotid artery displaced posteromedially and abutting less than 2,700. Tumor shows few cystic areas with intense heterogenous post-contrast enhancement

tracer uptake in the base of the skull and thoracic region corresponding to iso-hyperdense lesions in bilateral cervical, prevertebral, and mediastinum (Fig. 2). MRI neck and brain showed 53 × 44 × 49 mm, T2-hyperintense lesion arising in-between right carotids, encasing significantly ECA and ICA (Shamblin type II). The left side showed well-defined 9.8 × 7.4 mm T2-hyperintense lesion showing post-contrast enhancement splaying ICA and ECA (Fig. 3). Circle of Willis was found communicating/patent on MRA. The blood sample was sent for SDH-D and B mutation. The patient was planned for a staged procedure with surgical excision of the right CBT, and observation for the rest of the lesions with the decision to intervene if they turn symptomatic.

With adequate preoperative optimization and informed written consent, the patient was taken up for surgery. Under general anesthesia in Rose position, an oblique incision was made along the anterior border of the sternocleidomastoid, in a subplatysmal plane, tumor of around 6 × 5 cm was seen upon retracting sternocleidomastoid muscle laterally. Proximal control of CCA was taken, whereas distal control of internal carotid artery (ICA) and external carotid artery (ECA) was impossible immediately due to large size of tumor and encasement of vessels. Partially encased ICA was identified posterolaterally, after taking distal control, dissection was done using bipolar cautery in subadventitial plane. External carotid artery was displaced posteromedially, and distal control was taken by tracing its branches, and tumor was excised in craniocaudal direction in a subadventitial plane with blood loss of 400 mL (Fig. 4). On extubation, vocal cords were mobile. His postoperative course was uneventful. The patient was discharged on antihypertensive and β-blocker. After 2 weeks of follow-up, he was comfortable with normal pulse rate and BP. β-blocker was discontinued and continued anti-hypertensive. At 6 months, patient is doing well on antihypertensives and has no increase in size of the remaining lesions. His histopathology was reported as a CBT showing a classical Zellballen pattern (Fig. 5). His genetic testing report was positive for SDH-D novel mutation.

Discussion

Head and neck paragangliomas are rare, nonsecreting tumors. These tumors can be sporadic or familial with more than one-third of HNPGLs are associated with germline mutations even in the absence of family history. Hereditary syndromes are autosomal dominant, linked with mutations in the genes encoding the subunits of succinate dehydrogenase (SDH), i.e., succinate dehydrogenase B (SDHB), succinate dehydrogenase C (SDHC), succinate dehydrogenase D (SDHD)[3], and rarely seen in MEN 2, VHL, NF1. SDH-D mutation-linked cases are known to have multiple HNPGLS. In SDH-D, truncating mutations are most common.[4] Present case has rare single base deletion mutation L139Ffs*29 in exon 4, which is not reported in published literature. Evidence of malignancy is only accepted when there is metastasis to non-neuroendocrine tissue.[5] Shamblin in 1971 described the classification of CBT based on the invasion of carotid vessels.[6] Arya et al. described preoperative criteria to predict Shamblin classification of CBT on imaging. He described a method of measuring the angle of contact from the center of the ICA to tumor edge as an assessment of vascular encasement. Type I is an angle less than or equal to 180°, type II is an angle between 180° and 270° and type III angle greater than or equal to 270°. The relation of the tumor with ECA and CCA was not incorporated.[7] Surgery remains the mainstay of treatment for HNPG; alternative options being radiotherapy, chemotherapy,



Figs 4A to C: Operative steps (A) Showing skin incision marking over the anterior border of right sternocleidomastoid; (B) Large 6 × 5 cm lesion in the subplatysmal plane in between bifurcation of vessels, vagus nerve; (C) Post-excision showing intact ICA, ECA, hypoglossal nerve

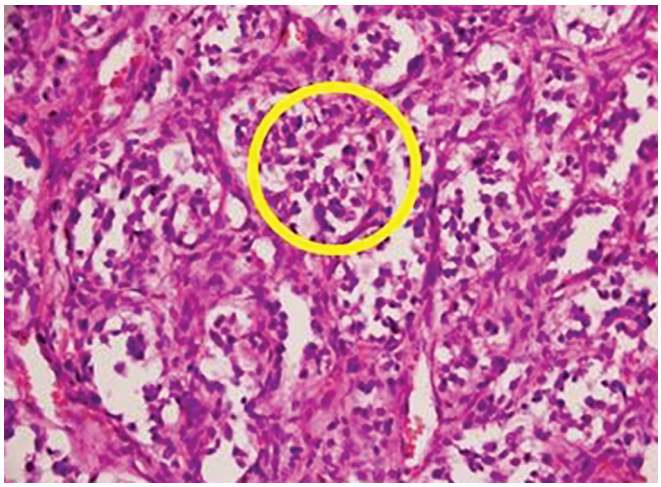


Fig. 5: Histopathology showing carotid body tumor showing classical Zellballen pattern

and watchful waiting.[8] The principles of CBT excision are adequate operative field exposure, proximal and distal vascular control, preservation of neurovascular structures, tumor excision in subadventitial plane using a bipolar energy source. If the tumor cannot be separated from ECA, ligation of ECA can be done and others include vascular shunting and grafting of the vessels.[9] Sporadic and familial PGLs need surveillance. Benn et al. reported age-related penetrance for SDH-D and SDH-B mutation carriers. Paraganglioma had developed in 48% of the carriers by age 30.[10] As SDH-D mutation exhibits maternal imprinting[11] surveillance of the sons of the affected father 10 years earlier than the onset of disease is necessary. The surveillance protocol is described in Table 1. Radiological evaluation is required to target the regions known for involvement in particular mutation.[12]

Conclusion

Head and neck paragangliomas are rare slow-growing non-functional tumors that can be sporadic or hereditary. Germline mutations involving SDH-D gene are known to have multiple tumors. Preoperative workup is essential. Bilateral CBTs should be excised in a staged manner to prevent loss of baroreceptor sinus reflux and result in labile hypertension. These tumors require annual surveillance.

Table 1: Showing the follow-up protocol for sporadic and familial paragangliomas

Follow-up	*Sporadic*	*Familial*
Clinical	Annually indefinitely	Annually
Hormonal	Annually for 10 years	Annual
Radiological	Annual neck USG for first 5 years Followed by once in every 5 years	USG/CT/MRI every 1–2 years targeting the regions associated with mutations DOPA-PET (if available)
Carriers		Exploration of carriers – a decade before the earliest age at diagnosis in the family[12]

Clinical Significance

Multiple CBTs with novel mutation are a rare clinical presentation.

Contributorship Details

Dr Jnaneshwari Jayaram provided the clinical photographs, wrote the manuscript in its first draft, and continued assisting in the editing process.

Dr Anita Dhar and Dr Anurag Srivastava provided the concept and guidance, critically reviewing the manuscript till the final draft.

Dr Suneha Kumari and Dr Kanika Sharma researched and edited the manuscript based on guidance from Dr Anita Dhar and Dr Anurag Srivastava.

Dr Shamim and Dr Hemant Sachani provided the imaging pictures and their interpretation.

Dr MC Sharma contributed to the pathological aspects of the manuscript.

All authors have read and approved the final manuscript.

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