Carotid Body Paraganglioma

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Abstract

Carotid body paraganglioma (CBP) is a type neuroendocrine tumour arising from paraganglial chief cells of carotid body. Situated at the bifurcation of the common carotid artery, it constitutes 0.5% of all body tumours. Though CBP's is most common paraganglioma of head and neck it is a rare neoplasm and requires a thorough examination for a proper diagnosis and therapeutic management. Here, we present a case of 36 year old female patient with CBP in left side of the neck.

Keywords: Carotid body, chief, management, neuroendocrine tumors, paraganglioma, sustentacular cells

Introduction

Paragangliomas comprise of a family of tumors of sympathetic and parasympathetic paraganglia.[1] Most of the sympathetic paragangliomas arise within adrenal glands and abdomen which are called pheochromocytomas and abdominal paraganglioma, respectively. However, parasympathetic paragangliomas are predominantly found in head and neck regions. The prototypical parasympathetic paraganglion is the carotid body, which is a small oval structure situated on either side of the neck within the semi-adventitia of the common carotid artery at the point of bifurcation into internal and external carotid arteries. It arises from the third brachial arch mesoderm and ectodermal-derived neural crest lineage.[2-4] The tumor originates from paraganglionic cells within it are termed as carotid body paragangliomas (CBPs). Other terminologies used in literature for CBPs are carotid body tumor, chemodectoma, glomus tumor, and nonchromaffin tumors.[5] It is the most common neuroendocrine tumor followed by jugulotympanic, vagal, and laryngeal paraganglioma that occur in head and neck region and constitute of <0.5% of all body tumors.[6] Rare cases of tracheal, interstellar, and parasellar paragangliomas are also seen.[4,6] CBPs are of familial and sporadic types with later being more common and showing autosomal dominant inheritance.[7] Majority of CBPs are asymptomatic in the initial phase as it appears as a slow growing and painless lesion unless there is involvement of regional neurovascular compartment.[4] Larger CBPs can cause symptoms such as syncope, dysphagia, odynophagia, hoarseness of voice including Horner's syndrome due to the involvement of carotid vessels and X–XII cranial nerves. The malignant transformation rate for this neoplasm is 6%–12% and shows no clear histologic changes.[4] This prompts for proper diagnosis of CBP using proper clinical and familial history, radiological, histopathological, and immunohistochemical aids. In cases with positive family history, multiple occurrence, previous history or current history of CBP, bilateralism and age <45 years, biochemical phenotype assay (adrenergic/nonadrenergic) and genetic testing (SDHD, SDHC, SDHB, and VHL) should be performed, so that it can contribute in early detection of complications and intervention, proper screening of family members and related tumors, as well as improvement in the overall prognosis of these patients.[7] Here, we present a case of 36-year-old female patient with CBP in the left side of the neck.

Case Report

A 36-year-old female patient reported with swelling on the left side of the neck since one year that gradually increased to the present size. On clinical examination, a well-defined, firm, nontender swelling measuring approximately 4 cm × 3 cm was seen anterior to the sternocleidomastoid muscle (SCM) at the

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Access this article online

Quick Response Code:

Website: www.amsjournal.com

DOI: 10.4103/ams.ams_183_18

How to cite this article: Hosalkar RM, Khivasara JS, Swain N. Carotid body paraganglioma. Ann Maxillofac Surg 2019;9:423-8.

level of hyoid bone [Figure 1]. Radiological examination by ultrasonography (USG) neck showed well-defined hypoechoic solid mass present near the left carotid artery [Figure 2]. Based on the clinical and radiological examination, a diagnosis of carotid body neoplasm was put forward.

The patient underwent wide excision of the tumor with preservation of neurovascular bundle. Neck exploration was performed through incision made along the anterior border of SCM and by raising the subplatysmal plane after dividing the SCM. For exposure of the lesional area, the carotid sheath was incised. The tumor was found to engulf the carotid artery at its bifurcation [Figure 3]. The branches of external carotid artery (ECA) supplying the tumor were ligated [Figure 4a and b] along with cautery of feeder vessels using bipolar diathermy. Once hemostasis and dissection plane was achieved, encasement of ECA was relieved by excising tumor completely [Figure 4c]. Operative and postoperative period was uneventful, without neurological deficit. Based on our experience with this case, we suggest that the proposed treatment must be individualized to each patient. Issues to be considered before any therapeutic management should include patient age, medical comorbidities, location and size of the tumor, possible presence of synchronous tumors, and a history of progressive neurological dysfunction.

The tissue thus obtained was sent in for histopathological examination [Figure 5]. Microscopic examination revealed an encapsulated tumor mass composed of round to polygonal cells with granular eosinophilic cytoplasm and centrally placed nuclei arranged in nests and organoid zellballen pattern separated by fibrovascular stroma [Figure 6a and b]. Areas of congestion were also observed. For immunohistochemical analysis, biotin-streptavidin-horseradish peroxidase technique was used using mouse antisera to neuron-specific enolase (NSE) (Dako Corp., 1:1000) and synaptophysin (Biogenex, 1:200). Tumor chief cells were found to be immunoreactive to NSE [Figure 6c and d] and synaptophysin [Figure 6e and f].

Based on clinical, radiological, histopathological, and immunohistochemical examination, a diagnosis of CBP of the

Figure 1: Clinical photograph of the patient

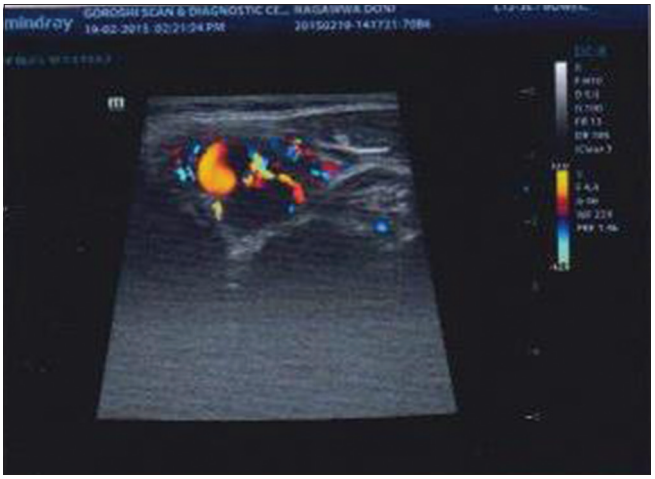

Figure 2: Ultrasonography showing a highly well-defined solid mass present situated near left carotid artery

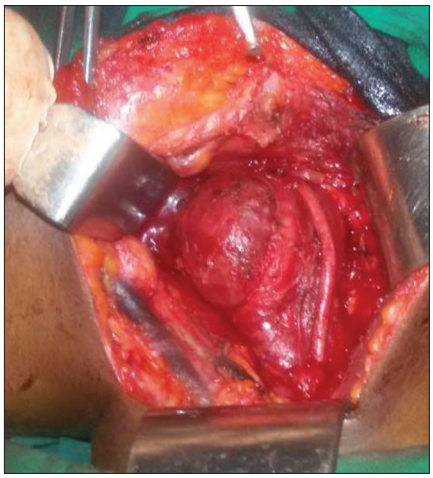

Figure 3: Intraoperative photograph showing tumor around bifurcation of left common carotid artery

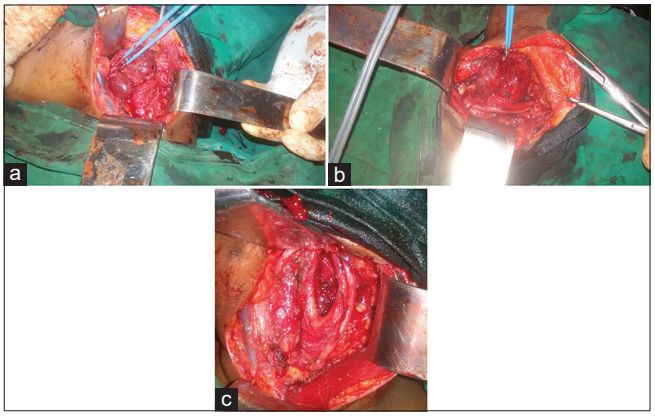

Figure 4: (a) Intraoperative photograph showing ligation of branches of external carotid artery, (b) intraoperative photograph during resection of carotid body paragangliomas after ligation of external carotid artery, (c) Intraoperative photograph after complete removal of tumor

left neck was given. The patient has been on follow-up for the last 6 months and no recurrence has been found [Figure 7].

Discussion

Carotid body is a reddish brown highly vascularized chemoreceptor organ, located within the adventitia posteromedial to the bifurcation of the common carotid artery into internal and ECA. Its function is related to the autonomic control of the respiratory and cardiovascular system as well as blood temperature. It increases the sympathetic flow thus controlling the autonomic drive primarily in the presence of hypoxia and to lesser extent in hypercapnia or acidosis.[8] It consists of two types of cells: chief cells and sustentacular cells which are derived from neural crest cells and neuroectoderm, respectively.[9] The tumors arising from the chief paraganglial cells are termed as paragangliomas and accounts for about 0.5% of all tumors. It accounts for 1 out of 30,000 head and neck tumors cases with 65% occurring in the carotid body region and are termed as CBP.[10] Sporadic and familial are two types of CBPs of which the sporadic form are most commonly seen.

CBP presents as a slow-growing mass, nontender mass situated anterior to the SCM at the level of hyoid bone. Seldom does the tumor transmit a carotid pulse or demonstrate a bruit/thrill. As the tumor increases in size, it may splay and encase the internal and external carotid arteries without narrowing them. Most of the CBPs remain asymptomatic, however, due to its close proximity to the adjoining nerves and vessels symptoms such as dysphagia, odynophagia, hoarseness of voice, or any other cranial deficit could be seen with increase in size. Some of the CBPs may attain a large size and infiltrate leading to the death of the patient. Due to vasoactive catecholamines produced by CBP, some patients may also present with hypertension, sweating, and headaches. The CBPs are most commonly seen in third to sixth decade of life and more prevalent in females as compare to males. Metastasis of the tumor could lead to the development of symptoms such as malaise, weight loss, or weakness.[3,11,12] The present case described a 36-year-old female having a swelling on the left lateral side of the neck that gradually increased in size and presented with no symptoms. CBP were classified by Shamblin and co-workers[13] into classes as given in Table 1 with later modification done by Luna-Ortiz *et al*.[14] as described in Table 2.

The exact cause of CBPs is not known. However, it has been suggested that chronic hypoxia and genetic predisposition could be one of the etiological factors [Figure 8]. Chronic hypoxia occurs in certain medical conditions such as cystic fibrosis, cyanotic heart disease, cirrhosis, and central alveolar hypoventilation at high altitudes. Chronic hypoxic stimulation causes carotid body chemoreceptor cells to overwork and compensate for the reduced oxygen levels, thus initiating hypertrophy of the chief cells followed by adaptive physiological (diffuse) hyperplasia, and ultimately may lead to pathological (focal) hyperplasia and/or neoplastic development.[15] Till date, 20 genetic mutations have been identified to be the cause CBPs of which the major are

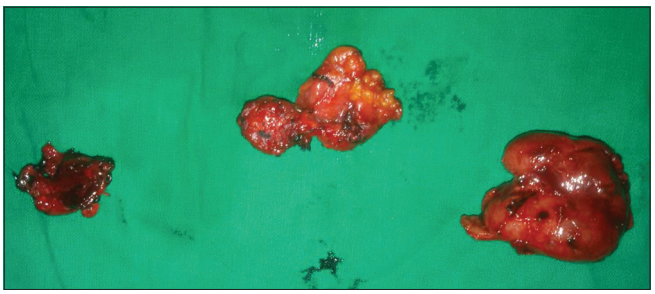

Figure 5: Photograph of the gross specimen of excised lesion

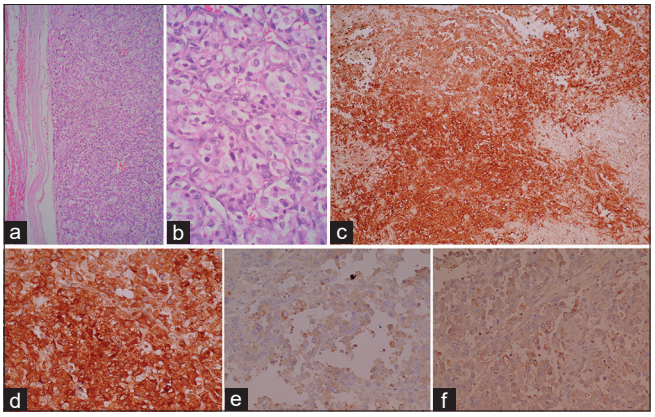

Figure 6: (a) Photomicrograph of soft-tissue section showing an encapsulated tumor mass composed of round to polygonal cells (H and E, ×40 Magnification), (b) Photomicrograph of soft-tissue section showing round to polygonal with granular eosinophilic cytoplasm and centrally placed nuclei arranged in nests and organoid zellballen pattern separated by fibro-vascular stroma with areas of congestion (H and E, 100× Magnification), (c) Photomicrograph showing immunoreactivity of neuron-specific enolase for chief cells in carotid body paragangliomas (×100), (d) Photomicrograph showing immunoreactivity of neuron-specific enolase for chief cells in carotid body paragangliomas (×400), (e) Photomicrograph showing immunoreactivity of synaptophysin for chief cells in carotid body paragangliomas (×100), (f) Photomicrograph showing immunoreactivity of synaptophysin for chief cells in carotid body paragangliomas (×400)

Figure 7: Clinical photograph of the patient on 6-month follow-up

Table 1: Shamblin's classification

Class	Features
I	Localized tumors with splaying of the carotid bifurcation, but little attachment to the carotid vessels. Complete surgical resection is generally possible with only minimal risk of vascular or cranial nerve complications
II	Tumors partially surround the carotid vessels. Complete resection is more challenging
III	Tumors intimately surround the carotid. Complete resection is very challenging and often requires temporary interruption of the cerebral circulation for vascular reconstruction. The risk of permanent vascular and neural defects is significantly higher than for Class I

Table 2: Modified Shamblin's Classification

Group	Features
I	Tumors <4 cm in size not surrounding or infiltrating the carotid and excision done without difficulty
II	Tumors > 4 cm in size partially surrounding or infiltrating the carotid and excision done with difficulty
IIIa IIIb	I, II, or III infiltration of carotid vessel >4 cm in size and intimately infiltrating or surrounding the carotid vessels with difficulty requiring vascular repair, sacrifice, or vessel replacement

NF1, RET, VHL, SDHC, SDHD, SDHB, EGLN1, KIF1B, SDHAF2, IDH, SDHA, TMEM 127, MAX, BAP1, EPAS1, FH, MDH2, and ATRX, respectively.[16,17] One such genetic study discusses the loss of function mutation in SDHC gene of Caenorhabditis elegans causing increased superoxide production and premature aging. This finding, along with other genetic studies performed in paragangliomas, suggests that reactive oxygen species (ROS), regulated by mitochondrial complex II may be involved in oxygen sensing and signaling in CBP. The defective mitochondrial complex II may instantly alter the levels of ROS thus modifying the cytoplasmic redox ratio which may in turn activate a cascade of events, including the inhibition of a potassium channel, membrane depolarization, increase in intracellular calcium concentration, and release of dopamine, which ultimately leads to carotid body discharge and hyperventilation within seconds. The constitutive activation of this pathway, triggered by the defective mitochondrial complex II in CBP, may be ultimately responsible for the hypertrophy, then hyperplasia, and eventually neoplastic growth of the CB.[15] Familial CBPs are associated with *de novo* germline mutations in tumor susceptibility genes, syndromes such as the multiple endocrine neoplasia type II syndrome, von Hippel-Lindau syndrome or occur spontaneously in hyperplastic glands, etc.[16,17] The present case did not show any genetic contribution nor any association with syndromes.

Clinically, CBPs proved to be a diagnostic challenge in 30% cases with the rarity of its presentation leading to unnecessary attempt at fine-needle aspiration cytology (FNAC), un-indicated biopsies, and explorative surgeries. FNAC with wide bore needle or biopsies could be dangerous as carotid artery aneurysms and

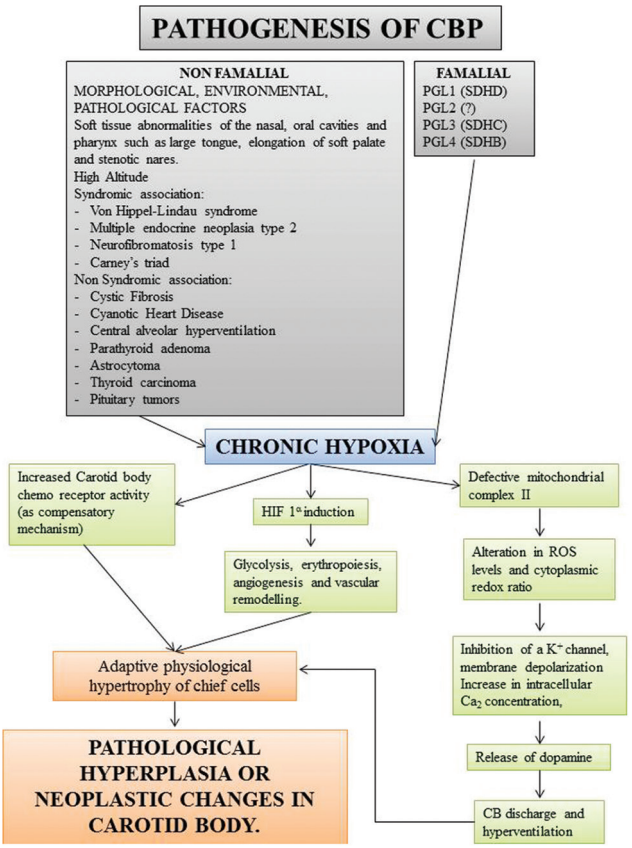

Figure 8: Pathogenesis for carotid body paraganglioma

elongation mimic CBPs. Furthermore, there is increased risk of hemorrhage. Hence, a proper multidisciplinary approach is needed for diagnosing CBP [Figure 9]. Radio-imaging techniques such as USG scanning, computed tomography, magnetic resonance imaging or arteriography, carotid arteriography along with serum and urine catecholamine level assessment can be performed for diagnosing CBP.[4,16] In the present case, following clinical examination, due to lack of facilities in rural setup, we performed a USG that showed highly vascular well-defined solid mass present near the left carotid artery. Blood investigation also showed increase in the catecholamine levels. Various neoplasms and diseases considered as a differential diagnosis for CBP are summarized in Table 3.[18]

CBPs microscopically shows two types of cells displaying typical nest-like or alveolar architectural pattern. Type I/chief cells are epithelioid cells often with enlarged hyperchromatic nuclei. The nuclei may appear pleomorphic and show multinucleated cells. These cells are arranged in solid groups called "Zellballen." Type II/sustentacular cells, usually surround the chief cells and are thought to be modified Schwann cells. Both types of cells lie within a dense network of capillaries.[5,11] In this case, the tissue biopsy obtained showed Type I cells in surplus. Although histopathology plays an important role in paragangliomas, immunohistochemistry helps in positive and accurate diagnosis.

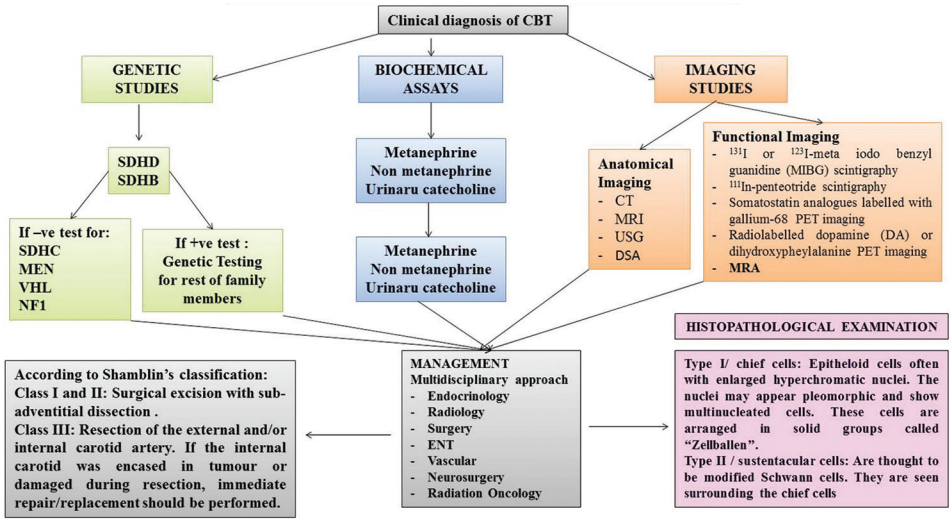

Figure 9: Diagnostic workup for carotid body paraganglioma

Table 3: Differential diagnosis for paraganglioma

Reactive	Infectious	Cyst	Neoplasm		Other
			Benign	Malignant	
Lymphadenitis	Bacterial	Dermoid cyst	Lipoma	Thyroid carcinoma (medullary and papillary)	Neck metastasis
Sjogren's syndrome	Tuberculosis	Epidermoid cyst	Hemangioma	Neuroendocrine tumor	Extracapsular extension of neoplasms
Castleman's or Kimura disease	Sarcoidosis	Brachial cyst	Lymphangioma	Hodgkin's lymphoma	
Sialadenitis	Cat scratch disease	Salivary gland cysts	Neurofibroma	Non-Hodgkin's lymphoma	
Sialolithiasis	Actinomyces	Thyroglossal duct cyst	Schwannoma	Oral squamous cell carcinoma of neck	
Thryoiditis	Tularemia		Desmoplastic fibroma		
Goiter	Parasitic		Paraganglioma*		
	Toxoplasmosis		Thyroid adenoma		
	Fungal		Teratoma		
	Coccidioidomycosis		Hyaline trabecular adenoma		
	Viral				
	Infectious mononucleosis				
	Mumps (parotitis)				

*This table depicts the clinical differential diagnosis of Paraganglioma as all these lesions or tumors share the common location in neck

These immunohistochemical markers include enzyme NSE; proteins stored in the secretory granules (chromogranin A and HISL19protein); resident proteins of the presynaptic vesicles; proteins of the cytoskeleton (neurofilament); catecholamines and indolamines (epinephrine, norepinephrine, dopamine, and serotonine); neuropeptides (enkephalin, VIP, and corticotropin); and molecules with unknown functions (PGP 9.5, myelin-associated glycoprotein Leu-7). The sustentacular cells may be identified by S100 protein, the cytoskeletal constituent glial fibrillary acidic protein; nerve growth factor receptor.[19] In immunohistochemical analysis for the present case showed chief tumor cells showing reactivity with synaptophysin and neuron-specific enolase stains. Surgical removal is the foremost choice of treatment modality in the management of CBPs. The treatment of choice also depends on the categorization of the tumor. According to Shamblin's classification Class I and II cases could be treated with surgical excision with subadventitial dissection while Class III cases required resection of the external and/or internal carotid artery. If the internal carotid was encased in tumor or damaged during resection, immediate repair/replacement should be performed.[13,14] Radiotherapy was a treatment of choice where age and medical factors were concerned along with cases where surgical resection could lead to increase in chances of morbidity.[2] CBP's metastasize in <2% of patients undergoing resection and only 6% of patients experience recurrence after complete resection. The incidence of malignant (metastasizing) CBPs ranges from 2% to 13% with sporadic types (12%) being more likely to be malignant than familial (2.5%).[5] For the reported case, a multidisciplinary approach was taken based on the results, wide excision of the tumor was done. Our patient is on follow-up for the past 6 months and does not show any sign of recurrence and metastasis.

Conclusion

Recent genetic discoveries in CBP may play a probable role in revolutionizing clinical patient management by providing

an opportunity for early tumor detection and intervention. CBP being a rare neoplasm mandates a thorough genetic, clinical, biochemical, radiological, histopathological, and immunohistochemical evaluation for its diagnosis and management.

The following few key points to remember:

- All CBP patients must be assessed for genetic mutations, and its implications should be explained to the patient and their relatives
- Familial CBPs have greater chance of multiple tumors, hormone secretion, malignancy hence needs a thorough assessment
- The management of CBP depends on assessment, including biochemical assays and detailed imaging. The treatment must be individualized for each patient.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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