

Carotid Body Tumor: A Review of the Literature and two Cases Reports in Baghdad Radiation Oncology Center, Medical City, Baghdad, Iraq

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ABSTRACT

BACKGROUND: The carotid body tumors are relatively rare tumor but constitute majority of head and neck paragangliomas about 70%. The purpose of this review article is to simplify understanding the

basic and clinical aspects of this challenging tumour, which is the first time study in Iraq.

CASE PRESENTATION: Two Iraqi people male and female presented with neck lump to Baghdad Radiation Oncology center. Radiotherapy performed for them as 50 Gy/ 25 fractions to treated conditions.

CONCLUSION: Throughout more than four decades working in this field, we faced 2 cases of CBTs, so it is very rare tumour. It is a challenging tumour management. Surgery is treatment of choice while radiotherapy is standard treatment for recurrent cases.

Key words: Carotid body tumour; Paraganglioma; Chemodectoma; Carotid angiography

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1. INTRODUCTION

Carotid body tumour (CBT) or chemodectoma is a rare, highly vascular, mostly benign tumour arising from the paraganglia of carotid body. CBTs are nonchromaffin paragangliomas arising from the chemoreceptor cells found at the carotid bifurcation. The tumour is highly vascular; its blood supply is the richest per gram of tissue of any tumour^[1]. The carotid body, which originates in the neural crest, is important in the body's acute adaptation to fluctuating concentrations of oxygen, carbon dioxide, and pH. The carotid body protects the organs from hypoxic damage by releasing neurotransmitters that increase the ventilatory rate when stimulated^[2]. The first anatomical description of carotid body was provided by Albrecht Von Haller in 1743^[2,3]. Histologically, carotid body tumors have a characteristic growth pattern often referred to as a zellballen^[4]. Carotid body tumors occur at any age but are typically diagnosed

between the third and sixth decades of life^[5]. The usual presentation is a slow growing mass at the angle of mandible^[2,4]. Carotid body tumors can be a diagnostic challenge for the clinician and lack of pre-operative diagnosis has been reported in up to 30% of the cases in different series^[4]. The diagnostic work-up of CBT may involve one or more of the following: Duplex US scanning, CT, MRI, MRA, carotid arteriography, and serum and urinary catecholamine level assessment^[2]. The treatment modalities for CBTs are surgical excision and/or radiotherapy^[5,6,7].

1.1 History

The first anatomical description of carotid body was provided by Albrecht Von Haller in 1743^[2,3]. Mulligan originally described CBTs as chemodectomas^[4]. The first attempt at surgical extirpation of carotid paraganglioma was by Reigner in 1880, but the patient died^[2,5]. In 1886, Maydl successfully removed the tumour, leaving the patient aphasic and hemiplegic. The first removal of carotid paraganglioma with preservation of carotid artery complex was by Albert in 1889 and in US by Scudder in 1903^[2,5]. In 1940 Gordon Taylor described a safe, sub adventitial plane of dissection^[5]. In 1957, the mortality and morbidity were so high that Hayes Martin recommended abandonment of resection of difficult tumours on proof of diagnosis^[4].

1.2 Anatomy

The carotid body originates from the third branchial arch mesoderm and from ectodermal-derived neural crest lineage^[2,3]. The carotid bodies, two in number, are situated one on either side of the neck, behind the common carotid artery (CCA) within its adventitia at its point of bifurcation into the external (ECA) and internal carotid trunks (ICA). Each CB weights 12 mg and is invested by a fibrous capsule and consists largely of spherical or irregular masses of cells, the masses being more or less separated from one another by septa which extend inward from the deep surface of the capsule^[1]. The carotid body is made up of two types of cells, called glomus cells: glomus type I (chief) cells, and glomus type II (sustentacular) cells. The carotid body contains the most vascularized tissue in the human body^[2]. This complex arrangement of blood vessels, nerves and gland-like tissue within the carotid bifurcation which comprises the carotid body. On gross examination the tumors are usually well-circumscribed and may have a pseudocapsule. The cut surface is typically solid with a smooth, rubbery texture but may display some areas of hemorrhage. The actual size of the tumor may vary greatly. Some have reported tumors as large as 10 cm^[6].

1.3 Histopathology

Histologically, carotid body tumors have a characteristic growth pattern often referred to as a zellballen, which refers to a well-developed nested growth pattern of the tumor cells with an intervening stromal component of delicate fibrovascular tissue and supporting cells at the periphery of the zellballen or cell nests. The tumor cells are round, hyperchromatic nuclei, a dispersed chromatin and abundant granular cytoplasm which may range from eosinophilic to basophilic in color. The tumor cells show reactivity with chromogranin and synaptophysin stains by immunohistochemical techniques along with other markers of neuroendocrine differentiation such as CD56 and neuron specific enolase^[6].

1.4 Etiology

The only known risk factors are the presence of chronic hypoxic stimulation and the genetic predisposition. The etiology is not

known^[4,5]. An increased incidence of CBTs in populations living at high altitudes and in patients with chronic obstructive pulmonary disease suggests a role of chronic hypoxia^[2,3,4,7]. It has been suggested to be an extreme degree of hyperplasia associated with high altitude hypoxia, however, no clear explanation for its occurrence at lower elevations has been put forward^[6]. Sporadic forms of carotid body tumors are more frequent, representing approximately 85% of CBTs, while familial forms account for about 10% of the cases in most series. The tumors are bilateral in 30% of the familial, but only 5% of the sporadic cases^[4]. The familial form is transmitted in an autosomal dominant pattern^[5].

1.5 Epidemiology

Carotid body tumours are very rare neoplasms constituting less than 0.5% of all body tumours. An incidence of 0.012% of all surgical specimens has been reported by a hospital-based study describing the paragangliomas of the head and neck region. About 5% of CBTs are bilateral and 5-10% is malignant, but these rates are much higher in patients with inherited disease. Familial tumors are found to be 5.8 times more common among patients who have carotid body tumors as compared with patients who have paragangliomas at other sites. The Mayo Clinic reported the largest series to-date, describing 153 cases over a period of 50 years^[4]. Male and female distribution is equal except at high altitude where females appear to predominate^[8]. The large literature on this tumor has indicated that the incidence of malignancy ranges from 2.6 to 50%, and the mortality rate is 8% in untreated cases. Metastasis, with a ratio considered to be approximately 5%, has been also reported, usually in the regional lymph nodes and uncommonly in the brachial plexus, cerebellum, lungs, bone, abdomen, pancreas, thyroid, kidney and breast^[3]. Overall prognosis is quite good with complete surgical resection^[6].

1.6 Pathophysiology

Carotid body tumours are typically slow growing mass lesions and are often present for years prior to the patient seeking medical attention. This lesion enlarges, it will encase, but not narrow the arteries. The tumour may attain a large size and infiltrative growth and local recurrence may lead to death. It have a malignant potential and it is not always possible to predict malignant behavior based on histological features alone^[6]. Due to close proximity of the tumour to the lower cranial nerves such as the facial, glossopharyngeal, vagus, accessory, hypoglossal and cervical sympathetic nerves; these nerves can be invaded by the tumour growth and expansion^[8]. Some researchers suggest that all CBTs be considered malignant because of their progressive involvement of local neurovascular structures^[4]. Although carotid body tumours occur at any age, they are typically diagnosed between the third and sixth decade of life^[5]. These tumors are nearly always nonfunctional, but catecholamine producing tumors do exist and can produce paroxysmal hypertension^[5]. The carotid body acts as a chemoreceptor^[2,3]. Carotid bodies are primarily responsive to hypoxia and to a lesser degree to hypercapnia and acidosis^[2] which induces reflex changes in vasomotor activity and respiration^[3].

1.7 Clinical Features

Carotid body tumors occur at any age but are typically diagnosed between the third and sixth decades of life^[5]. The usual presentation is a slow growing mass at the angle of mandible^[2,4,9]. Most are asymptomatic in the early clinical phase. Eventually, 75% of the patients develop symptoms such as neck pain, neck asymmetry, enlarging neck mass, hoarseness or syncope^[4,8]. These tumors are

nearly always nonfunctional, but catecholamine producing tumors do exist and can produce paroxysmal hypertension^[2,4,5,8]. Functional tumours can secrete histamine, serotonin, adrenaline and nor-adrenaline^[4]. On physical examination, CBTs typically present as a non-tender, rubbery, pulsatile mass. The mass can be displaced laterally but not vertically, due to carotid artery adherence, which is known as a positive Fontaine sign^[5,8]. An audible bruit (uncommon)^[2,5,9] or a pulsatile character of the mass suggests further evidence of involvement of or proximity to the carotid bifurcation. Other systemic symptoms such as malaise, weight loss, or weakness may suggest metastatic disease. Tachycardia, palpitations, hypertension, and tremors may also occur. Neurological examination deficits of cranial nerves VII, IX, X, XI, or XII^[9] as cranial nerve involvement have been estimated as 20%^[3]. The differential diagnosis of CBTs are many, which include: (1) Bronchial cysts; (2) Salivary gland tumors; (3) Carotid artery aneurysms; (4) Malignant lymphoma; (5) Neurofibroma; (6) Tuberculosis lymphadenitis; (7) Metastatic carcinomas; (8) Lymphadenopathies; (9) Neurogenic tumors; (10) Medullary thyroid carcinoma.

1.8 Diagnosis

It must involve thorough evaluation for primary tumour of the thyroid, the oropharynx, and the nasopharynx is essential, since metastases to a cervical lymph node is a much more frequent cause of a neck mass than CBTs^[9]. Carotid body tumors can be a diagnostic challenge for the clinician and lack of pre-operative diagnosis has been reported in up to 30% of the cases in different series^[4]. Exploration and biopsy can be disastrous and should be avoided in the management of carotid body tumors^[3,4,9], while fine needle aspiration (FNA) cytology is usually inconclusive^[4]. The diagnostic work-up of CBT may involve one or more of the following: Duplex US scanning, CT, MRI, MRA, carotid arteriography, and serum and urinary catecholamine level assessment^[2].

1.8.1 Duplex US

Doppler sonography represents an inexpensive, non-invasive diagnostic tool frequently used as the first imaging step. It typically present as a solid, well- defined, hypoechoic tumor with a splaying of the carotid bifurcation^[7].

1.8.2 Computed Tomography CT scan

Computed tomography is needed to evaluate jugulo-tympanic paragangliomas. The extent of temporal bone destruction is important in the preoperative classification of these tumours and to choose the operative approach accordingly. It is also used to exclude other paragangliomas in other parts of the body and to detect metastases from advanced CBT^[7].

1.8.3 Carotid Arteriography

Carotid arteriography is the gold standard for diagnosis. It shows the high vascular mass with tumour blush causing splaying of carotid arteries. It should be bilateral to exclude a contralateral tumour. Digital subtraction angiography (DSA) provides an arterial (map) and identifies the blood supply and flow dynamics of the tumor^[7].

1.8.4 MRI

Magnetic resonance imaging (MRI) plays the most important role in the pre-therapeutic evaluation. It typically shows a hyper intense signal on T2-weighted images and a distinct contrast enhancement on the T1-weighted images. MRI also presents the exact extension of the tumor and its exact relationship to the carotid vessels. MRI

is performed in combination with a dynamic contrast enhanced magnetic resonance arteriography (MRA)^[7].

1.9 Treatment

The treatment modalities for CBTs are surgical excision and/or radiotherapy. Surgical removal is the treatment of choice. Controversy is faced everywhere and treatment options are varied opinion. Surgery is considered by many as the standard therapy as it provides an immediate and complete removal of the tumour^[2,10]. On the other hand, it is very slow growth tumour and that most of them are benign so-called (wait and scan). A third group recommended radiotherapy as a primary mode of management of CBTs to achieve a tumour growth control while avoiding the potential morbidity of surgical intervention^[9].

1.9.1 Surgery

Shambling classification is used to assess the difficulty of surgical resection: (1) Class I lesions consist of tumours easily isolated and dissected from the carotid vessels; (2) Class II lesions are more adherent to the adventitial layer and partially encircle the vessel at bifurcation; (2) Class III lesions are more densely adherent to the carotid vessels and completely encircle the carotid bifurcation^[2,9].

The routine use of preoperative embolization is controversial because of the potential neurologic complication. The apparent benefit of embolization should be weighed against the risk of stroke. Its current use is limited to tumours greater than 5 cm in diameter^[2]. The use of shunts during resection of CBTs is controversial. Moreover, for large tumours, a shunt may be placed through a common carotid arteriotomy before tumour dissection begins to decrease bleeding and prevent an interruption of cerebral blood flow in the event of vessel injury^[9]. A study from Portugal reported 4 cases of CBTs resected using an ultrasound dissector. They believe that this technique improves the safety of excision, decrease the technical difficulties, lower blood loss and shortens the operation time^[10]. Surgical challenge is the high vascularity and proximity to cranial nerves and major vessels make this tumour a challenge. Due to its location and high vascularity, this tumour should be diagnosed preoperatively; otherwise, it will face the surgeon with unusual difficulties which make the experience unforgettable. Much literature has been produced about this tumour in the last century with continuing controversy regarding its natural history, biological behavior, proper technique of excision, and the risk of morbidity and mortality^[1,10].

1.9.2 Radiotherapy

Depending on the size and location of the lesions, the indication for RT may be either: (1) Primary irradiation in the case of functional or other inoperability; (2) Adjuvant irradiation for R1 to R2 resections; (3) Irradiation of recurrence if there is progression after surgery.

The principal indications for radiotherapy as primary treatment for carotid paragangliomas includes extensive tumours where resection would result in significant morbidity as well as patient related factors such as age and medical condition^[2,12]. RT is effective in local control and is probably the treatment of choice for lesions that are large or erode bone, particularly in older patients. Conventional fractionated three-dimensional (3D) conformal radiation therapy with 45 Gy to 55 Gy is the norm. The clinical target volume (CTV) is restricted to the tumor region with a safety margin to cover microscopic extensions. Irradiation of paragangliomas produces control rates good as or even better than surgery. Many studies noted a recurrence rate 22% with doses of less than 40 Gy, whereas recurrences occurred in

only 1.4% with doses of more than 40 Gy. Stereotactic single-dose radiation and Gamma knife therapy have efficacy in the treatment of paragangliomas. The results are favorable compared to fractionated radiation, with excellent local control rates and acceptable side effects. The median tumor margin dose was 15 Gy with overall tumor control was 93% at last follow-up with an 88% actuarial tumor control 5 years after surgery. Irradiation of paragangliomas of the carotid glomus can acutely cause pharyngeal mucositis and chronically may lead to skin fibrosis and dryness of the pharyngeal mucosa the irradiated side^[9].

1.9.3 Chemotherapy

Chemotherapy is generally ineffective in patients with benign paraganglioma. Metastatic malignant paraganglioma may respond to chemotherapy; the combination of cyclophosphamide, vincristine, and dacarbazine has been used most frequently. A high dose of metaiodobenzylguanidine (MIBG), a radionuclide that is used in lower doses in diagnosis of catecholamine-secreting tumors, has generated interest as a therapeutic modality^[10].

2. CASE PRESENTATION No. 1

A 50 year-old female patient presented with a left neck mass. She was complain also from malaise and headache. Neck US showed a well-defined, hypoechoic mass with at carotid bifurcation. She was undergo left neck mass biopsy at August 2016 and the pathologist revealed the histology of carotid body paraganglioma. She was then referred to Baghdad Radiation Oncology Center. Radiotherapy given as 50 Gy in 25 fractions to her left neck mass.

3. CASE PRESENTATION No. 2

A 39 year-old male patient presented with a right side cervical mass. He was undergo right sided neck mass incisional biopsy at September 2016 and the pathologist revealed the histology of carotid body tumor. Slide review and immunohistochemistry done with same results. Carotid angiography done showed large well defined mass noted in right carotid sheath measuring 34 × 33 × 42 mm, displaced carotid vessels anteriorly with some splaying noted. He was referred by his surgeon for radiotherapy. So he was treated by 50 Gy in 25 fractions in Baghdad Radiotherapy Oncology Center.

4. DISCUSSION

Carotid body tumors are rare and uncommon entities may be found in unilateral or both sides of the neck and in both genders at the different rate of frequency, and they belong mostly to a benign group of tumors and their surgical management is technically challenging. The most common presentation in patients with CBTs is a slowly enlarging painless mass in the neck. Locally invasive growth of these tumors subsequently leads to cranial nerve deficits along with compression symptoms like Horner's syndrome, syncope, hoarseness and dysphagia since the carotid body functions as a chemoreceptor organ that is stimulated by hypoxia, hypercapnea, and acidosis, it is involved in the control of blood pressure, heart rate, and respiration^[1,5,7,8]. CBDs are slow growing painless masses localized in the neck, anterior to the sternocleidomastoid muscle at the level of the hyoid bone. As the tumour grows, dysphagia, odynophagia, dysphonia, and symptoms due to compression of cranial nerves IX to XII may be seen. The most commonly involved

cranial nerve is the vagus, up to one third of all cases will show cranial nerve palsies^[3,8].

US is the first non-invasive procedure which allows seeing that is vascular discrimination between the solid and cystic nature of the mass. Carotid arterial angiography is the most valuable diagnostic technique, it is the gold standard for diagnosis is carotid angiography, which serves both diagnostic and treatment purposes. MRI and CT angiography can demonstrate the extent of the tumor and its relationship to adjacent structures^[7,8].

There are many choices of treatment for CBDs including observation, surgery, external beam radiotherapy, and stereotactic radiotherapy. Surgery is the treatment of choice. The local control by surgery alone is approximately 85-100%. Most of the reports demonstrated local control with radiotherapy alone is approximately 80-90% comparable to surgery^[9,10].

Treatment with radiotherapy can achieve comparable local control and less morbidity than surgical resection in paraganglioma. Regarding definitive radiation treatment of CBTs. There are many techniques, protocols and radiation dose ranges of treatment. Although stereotactic radiotherapy has been increasingly used and their results have been generally accepted, conventional radiotherapy and 3D radiotherapy are still commonly used in the place where stereotactic radiotherapy is not available. Many reports used a radiation dose of 50 Gy in 25 fractions, with a daily dose of 2 Gy^[3,5,6]. Continued follow-up is necessary, however, as recurrence and metastasis may occur years later^[10].

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