Dopamine-secreting Carotid Body Paragangliomas- Biochemical Control with Radiotherapy

Abel Wah Ek Soh and Peng Chin Kek

Abstract

Head and neck paragangliomas that are exclusively or predominantly dopamine-secreting are rare. Surgery and/or radiotherapy are modalities for locoregional tumoral control. Little is known about the efficacy of radiotherapy for biochemical control in such tumors. We report a 62-year-old Chinese man with bilateral carotid body tumors which were exclusively dopamine secreting. The left-sided tumor invaded the skull base and encased the left carotid artery. Surgery was not performed due to high risk of morbidity and mortality. The patient received external beam radiotherapy to bilateral neck regions. Progressive decline and eventual normalization of urinary dopamine excretion was seen together with a slight reduction in tumor size. This is the first report demonstrating the efficacy of radiotherapy for both biochemical and locoregional control of functioning carotid body paragangliomas.

Key words: dopamine-secreting, carotid body tumor, paraganglioma, pheochromocytoma, radiotherapy

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Introduction

Pheochromocytomas are neuroendocrine tumors of neuroectodermal origin that produce, metabolize, and usually secrete catecholamines. Closely related tumors of extra-adrenal sympathetic and parasympathetic paraganglia are classified as extra-adrenal paragangliomas. Sympathetic paraganglia are symmetrically distributed along the paravertebral axis from high in the neck near the superior cervical ganglion to the abdomen and pelvis. Small sympathetic ganglia can also be associated with organs such as the urinary bladder and prostate gland. Parasympathetic paraganglia are primarily localized to the skull base and neck.

In the head and neck, paraganglia are concentrated in the area around the carotid body, the jugulotympanic region, and the vagal glomus (1). Highly vascular paragangliomas can arise from any of these tissues. Paragangliomas which produce catecholamines in amounts sufficient to produce signs and symptoms or positive results on biochemical testing are uncommon (2). Tumors that exclusively or predominantly secrete dopamine are even rarer. Such tumors usually have an extra-adrenal location and are often malignant with multifocal or metastatic disease (2, 3).

The management of head and neck paragangliomas include surgical resection, external beam radiotherapy, and stereotactic radiotherapy (1). Only a handful of purely dopamine-secreting carotid body tumors have been described in the literature (4-7). These are either treated with surgical removal or expectant management due to the advanced stage of the disease.

We describe a patient with exclusively dopamine-producing carotid body tumors who was treated with external beam radiotherapy and subsequently demonstrated both biochemical remission and locoregional control.

Case Report

A 62-year-old Chinese man presented with a left upper neck lump which had been slowly enlarging over a 20-year period. He also complained of left ear hearing impairment for the preceding 3 years, postural giddiness over the preceding 1 year, cough when eating or drinking, as well as hoarseness of voice. There was no significant weight loss or anorexia and he did not have symptoms of headache, palpitations or excessive sweating. There was no past history of
hypertension and no family history of pheochromocytoma or paraganglioma could be ascertained since he did not have any living relatives (he was an adopted child and was single).

On examination, he was emaciated, weighing 37.4 kg with a height of 1.53 m. Blood pressure measured 86/55 mmHg with a heart rate of 80 beats per minute. There was no demonstrable postural drop in blood pressure. Neck palpation revealed a 4 cm left upper cervical (level II) mass which was fixed, pulsatile, and non-tender. No blood pressure reduction was noted during palpation of the neck mass. He was able to speak in full sentences albeit a slurred speech. Left hemitongue atrophy and weakness of tongue found.

Computed tomography of the neck showed a 5.3 cm mass at the left carotid bifurcation (Fig. 1A), extending to the parapharynx, the left Eustachian tube, and the left skull base eroding into the left hypoglossal canal. There was another 1.3 cm mass adjacent to the right internal jugular vein. The impression was that of bilateral carotid body tumors. Analysis of 24-hour urine metanephrines and catecholamines demonstrated isolated elevation of urinary dopamine at 4,885 nmol/day [normal range: 425-2,612] (Table 1). Plasma dopamine level was concomitantly raised at 241 pg/mL [normal: <20]. The diagnosis of exclusively dopamine-secreting bilateral carotid body tumors was made.

Magnetic resonance angiography was performed with a view of possible surgical resection of the tumors and it showed that the left-sided tumor was encasing the left carotid artery (Fig. 1B). As elevated plasma or urinary dopamine are more often associated with malignant than benign pheochromocytomas, computed tomography of the chest, abdomen and pelvis was done to exclude the presence of multicentric or metastatic disease. This did not reveal any adrenal or ectopic sites of the tumor. I-131 metaiodobenzylguanidine (MIBG) scintigraphy demonstrated increased tracer uptake at the neck corresponding to the positions of the carotid body tumors, with no significant tracer uptake elsewhere in the body (Fig. 2). Genetic analysis was performed to look for mutation in the succinate dehydrogenase (SDH) subunits B and D genes. A known SDHD mutation, M11, which involves a G-to-C substitution in exon 1, was found.

In view of the high risk of operative morbidity and mortality and skull base involvement of the left-sided tumor, surgical resection was not performed and the patient was managed with external beam radiation therapy. He received external beam radiotherapy to bilateral neck regions—a total dose of 57.5 Gy delivered in 25 fractions over five weeks. No radiotherapy-related complications were experienced.

Over the subsequent few years, there was a progressive decline and eventual normalization of his urinary dopamine excretion (Fig. 3), demonstrating biochemical response to radiotherapy. This was accompanied with improvement in his resting blood pressure which increased to 116/69 mmHg eighteen months post-radiotherapy. Repeat computed tomography of the neck over the subsequent 3 years showed minimal decrease in sizes of both carotid body tumors (Fig. 4).

Table 1. 24-hour Urine Catecholamines and Metanephrines of the Patient at Presentation

<table>
<thead>
<tr>
<th>24-hour urine parameter</th>
<th>Result</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epinephrine</td>
<td>Below detection limit</td>
<td>3-109</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>223 nmol/day</td>
<td>89-473</td>
</tr>
<tr>
<td>Dopamine</td>
<td>4885 nmol/day</td>
<td>425-2612</td>
</tr>
<tr>
<td>Metanephrines</td>
<td>672 nmol/day</td>
<td>400-1500</td>
</tr>
<tr>
<td>Normetanephrines</td>
<td>1033 nmol/day</td>
<td>600-1900</td>
</tr>
</tbody>
</table>

Figure 1. A, Contrast-enhanced axial computed tomography image showing the bilateral carotid body tumors at presentation (indicated by white arrows). B, Coronal view of contrast-enhanced T1-weighted magnetic resonance image demonstrating the bilateral carotid body tumors at presentation (indicated by white arrows).
Figure 2. $^{[131]I}$-metaiodobenzylguanidine scintigraphy showing increased tracer uptake over bilateral neck regions corresponding to the carotid body tumors.

Figure 3. Trend of the patient’s 24-hour urinary dopamine levels [in nmol/day] (normal range indicated by the dotted lines).

Discussion

Paragangliomas are usually diagnosed in the following clinical settings: 1) presence of symptoms and signs related to catecholamine hypersecretion, 2) presence of mass effect symptoms (for example in the case of head and neck paragangliomas), 3) incidental discovery on imaging, and 4) during family screening for hereditary paragangliomas (8). In the Mayo Clinic’s series of benign paragangliomas diagnosed over a 20-year period, 69% of the paragangliomas were found in the head and neck region. Most of these patients presented with mass effect symptoms or an incidental imaging finding (9). In this series, 20% of the paragangliomas were documented with catecholamine hypersecretion and the majority of these were localized to the abdomen and pelvis. Only 3.6% of the head and neck paragangliomas had catecholamine hypersecretion.

Dopamine-secreting paragangliomas

Evaluation of the biochemical phenotype of paragangliomas mainly reveals hypersecretion of norepinephrine and/or dopamine. Extra-adrenal paragangliomas rarely secrete epinephrine, reflecting a decreased expression of phenylethanolamine-N-methyltransferase, the enzyme that converts norepinephrine to epinephrine (10). Tumors that
produce dopamine either exclusively or predominantly are rare. They are usually found as extra-adrenal paragangliomas (11) and can be located in the carotid body, retroperitoneum, and pelvis. The predominance of dopamine and the relative lack of production of other catecholamines in these tumors are due to the deficiency of dopamine-β-hydroxylase, the enzyme that converts dopamine to norepinephrine (10).

In contrast to patients who harbor norepinephrine and/or epinephrine-secreting tumors, subjects with exclusively dopamine-producing tumors lack the classical presentation of paroxysms of headache, palpitations, diaphoresis, and hypotension. Most dopamine-secreting pheochromocytomas or paragangliomas have been associated with normal blood pressure (12-15) or hypotension (6). In the series of Proye et al, all three patients with exclusively dopamine-secreting pheochromocytomas were normotensive (11). In addition, these patients exhibited a dramatic drop in their blood pressure with α-adrenergic blockade. High doses of dopamine have been postulated to cause hypotension via reduction in venous return and inhibition of the vasoconstrictor effects of norepinephrine (6, 11).

The diagnosis of purely dopamine-secreting pheochromocytomas or paragangliomas would be missed if urinary dopamine is excluded during catecholamine screening. In one series, only 54% of patients were screened for benign paragangliomas prior to surgery (9). Purely dopamine-secreting pheochromocytomas may thus be undiagnosed due to the absence of symptoms. It may be prudent to evaluate all patients with suspected pheochromocytomas or paragangliomas for elevated catecholamine production. This recommendation has also been suggested by van der Mey et al for the management of carotid body tumors (16). Compared to urinary dopamine, plasma methoxytyramine (an O-methylated metabolite of dopamine) has been reported to be a better marker for tumors that secrete predominantly dopamine (2).

Elevated plasma and/or urinary dopamine are more often associated with malignant than benign pheochromocytomas (2, 17, 18). Increased excretion of dopamine was shown to predict malignant potential in preoperative patients with apparently non-metastatic paragangliomas (19). Thus imaging to exclude the presence of multicentric or metastatic disease should be performed once the biochemical diagnosis is made. Some dopamine-secreting pheochromocytomas or paragangliomas may not be enhanced on MIBG scans (11, 20). For such tumors, 18F-fluorodeoxyglucose positron emission tomography scanning may be useful for the detection of metastatic disease (21).

Disease-causing mutations in three genes (succinate dehydrogenase [SDH] subunits B, C, and D) encoding subunits of mitochondrial complex II-SDH are responsible for most cases of familial paragangliomas (22-25). Familial paragangliomas are inherited in an autosomal dominant fashion for all genes, although there is incomplete penetrance for SDHD mutations depending on whether the abnormality is inherited through the mother or father. Only individuals who inherit an SDHD mutation from the father are at risk to develop paragangliomas, although they may pass the mutation to offspring (23, 25). According to the genetic testing algorithm recommended by experts at the First International Symposium on Pheochromocytoma (26), testing for SDHB and SDHD mutations is suggested for patients who present with bilateral extra-adrenal tumors. SDHB mutations have been associated with malignant disease (27), extra-adrenal paragangliomas (28), and other extra-paraganglial tumors, for example renal cell carcinoma (29). A preponderance of head and neck paragangliomas and multifocal disease has been reported in SDHD mutations (23, 25), as in the present patient. In contrast to SDHB mutations, SDHD mutations are infrequently associated with malignancy (23, 25).

**Carotid body paragangliomas**

The carotid body is the most common site of paragangliomas occurring in the head and neck region. Carotid body tumors classically present as asymptomatic enlarging lateral neck masses. With enlargement, compression may result in symptoms related to cranial nerve and sympathetic
Management of dopamine-secreting carotid body paragangliomas

Unlike other catecholamine-secreting tumors, α-adrenergic blockade is not indicated for purely dopamine-secreting paragangliomas due to the absence of hypertension and/or the presence of hypotension. Preoperative α-blockade can aggravate hypotension and may even cause cardiovascular collapse (30). The choice of treatment depends on various factors including the location and extent of the tumor, the presence of multiple tumors, the age and health of the patient, and the preference of the patient and attending physician (31).

Surgery has been considered as the treatment of choice for carotid body paragangliomas. Complete resection of carotid body paragangliomas can be challenging due to tumor size, tumor vascularity, and tumor adherence to local vascular structures and the lower cranial nerves. Although surgical results have improved in relation to the incidence of cerebrovascular accidents and mortality, the rate of postoperative cranial nerve dysfunction can be as high as 50% (32). A multidisciplinary approach, involving the vascular surgeon, the head and neck surgeon or otolaryngologist, and/or preoperative embolization, has been advocated to decrease surgical morbidity (33).

Radiation therapy is the alternative therapeutic modality. Radiotherapy has been advocated for those with multiple paragangliomas to minimize the risks of multiple surgeries (31). In view of the high risk of operative morbidity and mortality as well as skull base involvement of the left-sided tumor in our patient, we elected for radiation therapy. Overall, the rate of local tumor control after radiotherapy has been estimated at 90% (31). All published series of head and neck paragangliomas treated with radiotherapy have reported on clinical response based on locoregional control and distant recurrences with no mention of the control of catecholamine hypersecretion (34-42). There is only one case report demonstrating control of tumor growth and reduction in the plasma and urinary norepinephrine levels in a norepinephrine-secreting glomus jugulare tumor after intravascular embolization and radiation therapy (43). We have, on the other hand, demonstrated that biochemical remission was achieved post-radiotherapy with progressive decline and eventual normalization of the present patient’s urinary dopamine excretion even without complete regression of the carotid body tumors. This was coupled with clinical improvement in his blood pressure which rose to the normal range as dopamine hypersecretion abated. Paragangliomas usually remain stable in size or partially regress after successful radiotherapy (31). In our patient, the biochemical remission achieved despite minimal reduction in tumor size could be attributed to increased susceptibility of the secretory mechanisms of the tumor cells to damage by radiation in comparison to the apoptotic effects of radiation on the tumor cells.

In conclusion, carotid body paragangliomas that purely secrete dopamine are rare tumors and their clinical presentation differs from norepinephrine and/or epinephrine-producing paragangliomas. Evaluation of catecholamine hypersecretion will therefore be necessary for all patients. The present case demonstrates that external beam radiotherapy is not only effective in controlling the local progression of carotid body paragangliomas, but it is also useful for the biochemical control of such tumors which are functional.

The authors state that they have no Conflict of Interest (COI).

References


