Carotid Body Tumor as a Reversible Cause of Syncope

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The causes of syncope are diverse and extensive; carotid body tumors are an extremely rare cause of syncope. These rare neoplasms represent less than 0.5% of all head and neck tumors. The authors present a case of a woman with syncope who was found to have a right-sided carotid body tumor. After surgical resection was performed, she did not have any additional syncopal or near-syncopal events. The authors provide a review of the literature on the natural history, presentation, and preferred management of carotid body tumors. With modern diagnostic tools and treatment options, most patients with this diagnosis can expect to recover fully.

In the current report, we present the case of a patient with syncope who, after other causes had been ruled out, was found to have a right-sided carotid body tumor as the cause of her condition. We also review the history, presentation, epidemiology, etiology, diagnosis, management, and prognosis of this condition.

Report of Case

Our patient was a 75-year-old white woman with a medical history that included hypertension, type 2 diabetes mellitus, and a prolapsed bladder. She was admitted to the hospital with a chief complaint of syncope and left hip pain secondary to her fall. She reported having approximately 4 or 5 near-syncopal episodes before this admission. These earlier events consisted of a sensation of dizziness but did not result in loss of consciousness or postural tone. However, they were increasing in frequency. The patient reported that the events were occasionally linked to her position (ie, standing) and occurred at different times throughout the day. She had no history of seizures or stroke.

Her syncopal episode occurred while she was standing at the sink in her bathroom. She reported experiencing a prodrome of dizziness before falling to the floor. She stated that she had a rapid recovery, crawled to the toilet for positional support, and then called out to her family members, asking them to phone for emergency medical services. The patient was neither disoriented nor weak after the episode and had no associated bowel or bladder incontinence or any oropharyngeal trauma. Although she had type 2 diabetes mellitus, she was normoglycemic at her home when she was tended to by emergency medical services.

During physical examination at admission, the patient appeared to be her stated age and was in no acute distress; she was awake, alert, and oriented. Her vital signs were stable. Her neck was not obese, enabling the physician (P.H.S.J.) to palpate a small, pulsatile right-sided mass with some mild tenderness to light pressure. Except for this finding, the physical examination findings were within normal limits for the patient’s age.

On day 1, several diagnostic studies were performed. An electrocardiogram exhibited normal sinus rhythm; an echocardiogram showed an ejection fraction of 60% with mild, concentric left ventricular hypertrophy. Her orthostatic vital signs were unremarkable. Plasma metanephrine levels were mea-

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sured and were within normal limits. A computed tomographic (CT) scan of the brain without contrast material enhancement was unremarkable. The patient’s heart rate was monitored telemetrically and exhibited a sinus cardiac rhythm throughout her hospital stay.

On day 2, results from magnetic resonance (MR) imaging of the brain, performed with and without gadolinium contrast enhancement, demonstrated no acute changes or abnormal enhancement; only scant chronic white matter changes were noted. An MR angiogram of the brain was unremarkable. An electroencephalogram was within normal limits and showed no areas of focal slowing and no spikes or sharp wave activities. Results from duplex Doppler carotid ultrasonography revealed normal carotid and vertebral arteries; it also demonstrated a 1.5-cm nodule that was near the thyroid gland but situated between the bifurcation of the right common carotid artery into the right internal and external carotid arteries.

On the third day, 3-dimensional CT angiography of the neck and CT of the neck with iopamidol contrast enhancement (Isovue-370, 100 mL) was performed, and results from these tests demonstrated a 1.7-cm mass with an intense vascular blush at the bifurcation of the right common carotid artery (Figure 1). The findings were deemed to be consistent with a carotid body tumor.

The vascular surgery department was consulted on day 3 and recommended surgical resection of the tumor. The patient was informed of the risks and benefits of the procedure and agreed to proceed. The operation was uncomplicated.

At resection, the tumor appeared to be a highly vascularized, solid mass resembling a tuft of capillaries. It was sent to the pathologist for histologic analysis. Histologic findings were typical of a carotid body tumor and indicated no signs of malignancy. Sections of the tumor appeared highly vascular, with cells palisaded by surrounding blood vessels. There were numerous cell clusters in zellballen formation, separated by a prominent vascular stroma that is pathognomonic for carotid body tumors. Hematoxylin-eosin staining revealed chief cells—type I cells that are APUD (amine precursor uptake and decarboxylation) cells with copious cytoplasm and large round nuclei (Figure 2), and S100 staining revealed the elongated type II supporting cells (Figure 3) that are also found in carotid body tumors.

The patient had no postoperative complications and exhibited no nerve damage or deficits. She was closely followed up for 15 months after hospital discharge and had no additional syncopal or near-syncopal episodes.

Comment and Review of Literature

Historical Background

A carotid body tumor is a rare neoplasm of the carotid body that was first described by Lushka in 1862.10 In 1880, Riegner attempted the first surgical resection, which resulted in the death of the patient.11,12 Maydl’s resection attempt in 1886...

Figure 1. Three-dimensional computed tomographic (CT) angiogram (A) and transverse CT scan (B) of the neck of a 75-year-old woman presenting with complaint of syncope. The images revealed a 1.7-cm carotid body tumor (arrows) at the bifurcation of the right common carotid artery.
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Figure 2. Histologic analysis of a tumor in a 75-year-old woman revealed numerous chief cells in the pathognomonic zellballen cluster formation (arrow), separated by a vascular stroma (hematoxylin-eosin stain; original magnification, ×40).

Figure 3. Histologic analysis of a tumor in a 75-year-old woman revealed elongated sustentacular cells that are pathognomonic for carotid body tumors (S100 stain; original magnification, ×40).

was reportedly successful, but the procedure caused substantial, irreversible residual complications of aphasia and hemiplegia in his patient. The first published report of resection of a carotid body tumor with preservation of the carotid arteries was by Scudder in 1903. In 1940, Gordon-Taylor illustrated an appropriate plane of dissection for the procedure. In 1953, Morfit et al described arterial reconstruction techniques, offered operative recommendations, and provided the first documented report of a successful carotid body tumor resection. A major publication by Shamblin et al provided a reliable template for categorizing carotid body tumors based on the degree of encirclement of the carotid arteries, a system that is still used today.

Although carotid body tumors have been reported in the literature for many years, syncope has rarely been mentioned as a manifestation of these tumors. In 1947, McSwain and Spencer described 2 patients in whom syncope was the presenting sign of carotid body tumor. In 1967, Farr described 37 patients with carotid body tumors, including only 1 who presented with syncope. On the basis of our literature review, instances of syncope as a presenting sign of a carotid body tumor in more recent literature continue to be rare and exceptional.

**Presentation**

Classically, patients with a carotid body tumor present with a slowly enlarging, painless neck mass, which is often anterior to the sternocleidomastoid muscle at the level of the hyoid. These tumors are attached to the carotid sheath and have limited vertical mobility and permissive lateral mobility. Occasionally, pulsation can be palpated immediately anterior to the lesion and is caused by the external carotid artery. Rarely, carotid body tumors secrete catecholamines, which can result in hypertension. Our patient’s metanephrine levels were within normal limits, and she did not exhibit any hemodynamic instability. The majority of patients with carotid body tumors are asymptomatic until the tumor enlarges; carotid body tumors expand slowly, with a growth rate of 0.5 cm per year. Syncope, dizziness, and transient ischemic attacks are very rare presentations. More frequent presentations are neck discomfort, dysphagia, or dyspnea due to the size of the mass, or hoarseness, dysphagia, or tongue weakness due to cranial nerve involvement. Specifically, the 8th through 12th cranial nerves may be involved. Involvement of the mandibular branch of the seventh cranial nerve has been reported but is rare. Williams et al described 30 patients with carotid body tumors, none of whom presented with syncope. Singh et al, in their study of 10 patients with carotid body tumors, discovered similar findings. The lack of syncope as a presenting feature of carotid body tumor was also evident in the study by Kraus et al of 15 patients with carotid body tumors. To our knowledge, it was McSwain and Spencer who first described syncope as the presenting manifestation of a carotid body tumor. As previously mentioned, Farr, in a study of 37 patients, reported only 1 patient in whom syncope was the presenting feature. Typically, patients with carotid body tumors are initially unaware of their diagnosis and are free of pain or discomfort until the tumor is larger than 1 cm.

**Epidemiology**

Syncope is a relatively common diagnosis. In one of the largest studies that evaluated the incidence and prognosis of
syncope, in which 7814 men and women were followed up for an average of 17 years as part of the Framingham Heart Study, 860 (11%) had syncopal episodes.24 The incidence of syncope was similar in men and women; approximately one-third of individuals were likely to have a syncopal episode in their lifetime.24

As previously discussed, syncope due to a carotid body tumor is extremely rare, and very few patients with this presentation have been described. Carotid body tumors may occur at any age but are most commonly diagnosed between the third and sixth decades of life.18,25 They seem to be slightly more common in women, and most patients are white.26 In Farr’s study8 over a 40-year period, the tumors were more prevalent in neither men nor women, and the average age at onset of symptoms was 46 years (range, 19-72 years). Williams et al,10 in their study of 30 patients, noted similar epidemiologic characteristics. Some reports have suggested an association between high altitudes and hyperplasia of the carotid body, usually occurring at or above a threshold level of 1500 m above sea level.2,5,20,27-29 Our patient, however, lives in a city approximately 600 m above sea level. In addition, multiple carotid body tumors and bilateral presentation have been associated with a positive family history.11 Carotid body tumors are bilateral in 10% of cases, and 30% of patients with bilateral tumors have a positive family history.30

Etiologic and Pathologic Characteristics
The carotid body is a physiologically important paraganglion.9,20 It responds primarily to hypoxia by detecting the hydrogen ion concentration and feeding back to the respiratory center in the medulla, which sends impulses to the external intercostal muscles, diaphragm, vasculature, and heart, thus reflexively increasing the rate and depth of ventilation, as well as slightly increasing blood pressure and heart rate.4,9,11,22 Embryologically, the carotid body arises from a combination of the third branchial arch mesoderm and ectodermal-derived neural crest cells.4,11 Histologically, carotid body tumors are well vascularized and nonchromaffin in appearance.7 The carotid body is multilobular and comprises 3 types of cells, each of which is responsive to hypoxia. Type I cells, or chief cells, produce catecholamines and immunoreactive peptides and are arranged in a typical cluster formation called zellballen. Type II cells, also referred to as sustentacular cells, surround the type I cells and have characteristics similar to those of Schwann cells. Type III cells are sensory nerve endings that function as the afferent limb for chemoreceptor reflexes by means of the carotid sinus nerve to the respiratory control center.20,25

Before 1988, neoplasia was the only documented pathologic state affecting the carotid body. In more recent literature, chronic hypoxemia has been described as a stimulus for hyperplasy and hyperplasia of the carotid body.22,31 The descriptive term chemodectoma (meaning “of chemoreceptor origin”), originally coined by Mulligan in 1951, is sometimes used in more dated literature to classify carotid body tumors.4,11,32,33 However, carotid body tumors are more accurately termed paragangliomas because they arise from paraganglionic cells, which are epithelial cells of neural crest origin that migrate closely with the autonomic nervous system’s ganglion cells.4,11

The paraganglioma, or carotid body tumor, encases the carotid bulb and may subsequently compress the surrounding anatomic structures, including the cranial nerves and the sympathetic chain.11 Typically, as evidenced by the rarity of syncope as a manifestation of carotid body tumor, disruption of the carotid body by a tumor does not physiologically impair consciousness. The carotid sinus, located adjacent to the carotid body, maintains blood pressure and pulse in response to postural changes; its compression by a mass can lead to both orthostatic hypotension and failure of the heart rate to increase, and thus plausibly lead to syncope.8

Carotid body tumors are classified into 2 forms: sporadic and hereditary. The sporadic form is more common and tends to occur slightly more often in women than in men.24 The hereditary form accounts for roughly 30% of cases and is equally common in both sexes.20 Carotid body tumors are bilateral in 5% of sporadic cases and in 33% of hereditary cases.34 Germ-line mutations in what have been identified as the paraganglioma susceptibility genes, notably PGL-1 and PGL-2, have been attributed to heritable carotid body tumors, even in the absence of family history.20,33 These genes encode for the succinyl dehydrogenase (SDH) enzymes, particularly the SDH-D and SDH-B subtypes. The SDH enzymes have been mapped to 4 chromosomal loci. Each of the subtypes has a dominant mode of inheritance with penetrance that may be linked to both age and degree of hypoxia. The genes PGL-1 and PGL-2 display maternal imprinting (inactivation); hence, genes carrying a mutation that may manifest as carotid body tumor are inherited only from the father.20,35,36 Although the prevalence of these genes is low, patients who have them almost invariably present with multiple tumors.33,37

Diagnosis
Carotid body tumors may be diagnosed or suspected from a patient’s history and physical examination findings, but the diagnosis is confirmed by imaging studies.20 Approximately 1 in 30,000 tumors of the head and neck is a paraganglioma, and the most frequent site is the carotid body (45%).25 A high index of suspicion is important in the diagnosis of carotid body tumor.17 The differential diagnosis is manifold and includes branchiogenic cyst, aberrant thyroid gland, neurofibroma, cervical node hyperplasia, lymphoma, metastatic carcinoma, aneurysm, deep-lobe parotid enlargement, and arteriovenous malformation.7,11,19,30 In most cases, such diagnoses can be excluded with ultrasonography.7 Moreover, the initial use of such noninvasive modalities provides excellent information in the workup of a neck mass, specifically in depicting the distortion of the internal and external carotid arteries secondary to the mass effect of a carotid body tumor.4,19,20,22,38
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Widening of the carotid bifurcation with a well-defined tumor blush is virtually pathognomonic from a radiologic perspective.\(^9,11,19\) Bilateral studies enable the detection of multicentric disease\(^12,39\); this approach was used in our case. Computed tomographic angiography is consistently described as the most valuable study in the diagnosis of a carotid body tumor;\(^39\) and our experience supports this judgment. It is the most accurate modality and is the reference standard in the diagnosis of carotid body tumors.\(^4,9,19,25,40\) This diagnostic study discloses important details, including unsuspected contralateral tumors, the need for preoperative embolization, and the degree of atherosclerosis in the carotid artery.\(^11,20\)

Fine-needle aspiration is not useful in the evaluation of carotid body tumors.\(^9,17,20,41\) Open biopsy should also be avoided because it may result in substantial hemorrhage from these highly vascular tumors.\(^9,11\) Urinary or serum screening for metanephrines is not necessary but is occasionally performed if the patient is exhibiting vasomotor instability or hypertension.\(^4,11,30\)

In 1971, Shamblin\(^15\) developed a classification system based on the relationship between the carotid body tumor and its adjacent vessel walls that helps predict surgical outcome on the basis of angiographic findings. This system yields 3 groups of tumors, as follows:

- **Group I**—These tumors do not involve the vessel walls and are consequently easier to resect surgically. They are usually less than 5 cm in diameter and infrequently widen the carotid bifurcation. The tumor in the patient described in the present report was classified as group I.
- **Group II**—These tumors more intimately involve the adjacent vessel walls but do not encase them. They are often larger than 5 cm in diameter.
- **Group III**—These tumors are intramural and encase both the internal and external carotid arteries in addition to regional nerves. They are often larger than 5 cm in diameter.

Because group II and III tumors are often larger than 5 cm, these tumors often widen the bifurcation of the carotid arteries. A progression in the Shamblin group classification of a tumor correlates with an increased likelihood of regional nerve involvement as well as intraoperative and postoperative complications.\(^14\) This classification system is still used in the assessment and management of carotid body tumors.\(^9,11,14,17,20,25,33\)

**Treatment**

Since carotid body tumors were first discovered, there has been no consensus on the best treatment options.\(^5\) Currently, surgical resection is the mainstay of management if the patient’s surgical risk is acceptable, and resection should be performed early so that tumor size does not increase the risk.\(^9,14,17,20,30,33,42-46\) The rationales for resection include the following:\(^11,20;\)

- There is no reliable screening mechanism to follow the histologic progression of these tumors.
- The surgical risk in Shamblin group I tumors is minimal; some tumors are malignant at presentation.
- To our knowledge, spontaneous regression has never been reported.
- All carotid body tumors will eventually become symptomatic.

The surgical technique is well documented. Early proximal and distal control of the common, internal, and external carotid arteries is imperative. Identification of a relatively avascular plane between the tumor and artery is equally important for an uncomplicated course. The most widely recommended approach is subadventitial resection through the avascular space between the carotid vessels,\(^11,17,25,47\) as initially described by Gordon-Taylor.\(^13\)

Carotid body tumors are radiosensitive and may be managed with radiation therapy if necessary.\(^4,11,45-50\) The choice between surgery and radiation therapy is based on the risk of treatment complications and the anatomic presentation of the tumor.\(^7,11,17,20,22\) Radiation therapy does not completely remove the tumor. Instead, it provides a mechanism to halt further tumor growth.\(^33,42\) Tumors categorized as Shamblin group II or III are often associated with a higher rate of operative complications, especially for group II.\(^11,51,52\) Moreover, for patients with Shamblin group III tumors that present as technically difficult to resect or as unresectable, radiation therapy should be strongly considered.\(^7,11,17,20,22,25\) Despite the documented degree of surgical difficulty, successful resection of Shamblin group III tumors has been reported, although these procedures involved vascular reconstruction with synthetic grafts or autologous vein grafts.\(^17,25\) Recommendations in the literature advocate radiation therapy for patients with carotid body tumors stratified as Shamblin group III and for the management of residual tumor when resection is incomplete owing to the anatomic location of the tumor.\(^43,46\) Given that carotid body tumors are small, asymptomatic, slow-growing tumors that typically present in elderly patients, who are likely to have significant risk factors for surgical intervention or adverse reactions to radiation therapy, the tumors may be managed by observation alone.\(^9,11,17,33,45,46,53\)

**Prognosis**

Carotid body tumors grow slowly and have a doubling time of approximately 4 years.\(^34\) Accurate preoperative diagnosis in combination with modern surgical techniques yield excellent results with minimal complications in most patients.\(^11,33\) Furthermore, survival after resection is equivalent to that in age- and sex-matched control subjects.\(^11,21\) Without treatment, carotid body tumors may become life threatening because of their increasing size and associated effects.\(^11\)

Bilateral tumors occur in approximately 10% of patients with tumors, and 30% of patients with bilateral tumors have
a family history of bilateral tumors. Bilateral carotid body tumors, which have a genetic component, are known to occur. Patients with multiple parangangiomas should have extended follow-up, and their family members should be investigated as well, given the increased risk of complications and potential for metastatic disease.

Carotid body tumors often exhibit a locally aggressive and infiltrative growth pattern. Malignancy occurs in 6% to 12% of cases, ranking carotid body tumors as the most frequently malignant head and neck parangangioma. Metastasis most frequently involves the liver, bones, and lungs. Surgical excision of metastatic disease is often palliative and is considered the first-line treatment modality for patients who are cleared for surgery; minor postoperative neuropathies, if present, are transient.

Conclusion
Carotid body tumors are rare and often present challenges to physicians in diagnosis and management. Although they are a rare cause of syncope, spontaneous syncope with no other apparent cause should prompt evaluation for a neck mass. If no mass is palpable, ultrasonography of the neck, followed by CT angiography when indicated, may reveal a carotid body tumor. Surgical resection is the treatment of choice, but radiation therapy should be considered in patients with complicated tumors or contraindications to surgery. Treatment should be individualized, addressing the size and anatomic presentation of the tumor, patient demographics, and associated deficits secondary to the tumor. With the use of modern imaging and surgical techniques, most carotid body tumors can be safely removed, providing abatement of associated syncope.

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References


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