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Catecholamine-Secreting Paragangliomas at the Skull Base

Abstract—Paragangliomas (glomus tumors) comprise 15% of all neoplasms at the skull base. Despite extensive growth, these tumors usually do not secrete active biogenic substances into the circulation in sufficient quantities to produce symptoms. When they do secrete large amounts of catecholamines, they will cause symptoms that mimic a pheochromocytoma. The still confusing nomenclature of paragangliomas is reviewed, and the clinical work-up, surgical treatment, and follow-up of five patients with catecholamine-secreting paragangliomas of temporal bone (3), infratemporal fossa (1), and nasopharynx (1) are presented and discussed. (*Skull Base Surgery, 6(1):35–45, 1996*)

Paragangliomas (glomus tumors) comprise 15% of all the neoplasms that are found in the region of the skull base.[1] They usually arise from the paraganglia in the temporal bone, but occasionally occur closer to the central skull base. The incidence of functional activity in skull base paragangliomas is 1% to 2%.[2–4] In these cases the continuous or episodic secretion of catecholamines may cause clinical symptoms which can mimic a pheochromocytoma. When manipulated surgically, such a catecholamine-secreting paraganglioma (CSPG) may initiate a life-threatening hypertensive crisis and an anesthetic emergency.

Out of a series of 258 consecutive paragangliomas treated at the ENT department of the University Hospital of Zurich by the senior author from 1975 to 1991, five (1.9%) were catecholamine-secreting tumors (three of the temporal bone, one of the infratemporal fossa, and one of the nasopharynx).

This article serves two purposes. The first is to clarify the often confusing nomenclature associated with paragangliomas. The second is to review their treatment in five patients.

THE PARAGANGLION SYSTEM

It is now generally accepted that glomus tumors should be defined as paragangliomas, since glomus bodies belong to a system of paraganglia. Paraganglia are a collection of cells that are found widely distributed throughout the body. They are characterized by an intimate relationship to both the autonomic nervous system and major blood vessels. It is less known that paraganglia can be classified as either sympathetic and parasympathetic. This explains the existence of CSPG, as will be discussed (Fig. 1).

Sympathetic paraganglia are composed of modified second-order sympathetic neurons that develop no axonal budding but remain as a discrete collection of cells (Fig. 2). These cells contain dense-cored granules which are the storage centers for catecholamines that are released into the circulation. When sympathetic paraganglia cells are stained with potassium dichromate the dense-cored granules turn brown due to the presence of catecholamines. Thus the term *chromaffin cell* denotes a positive

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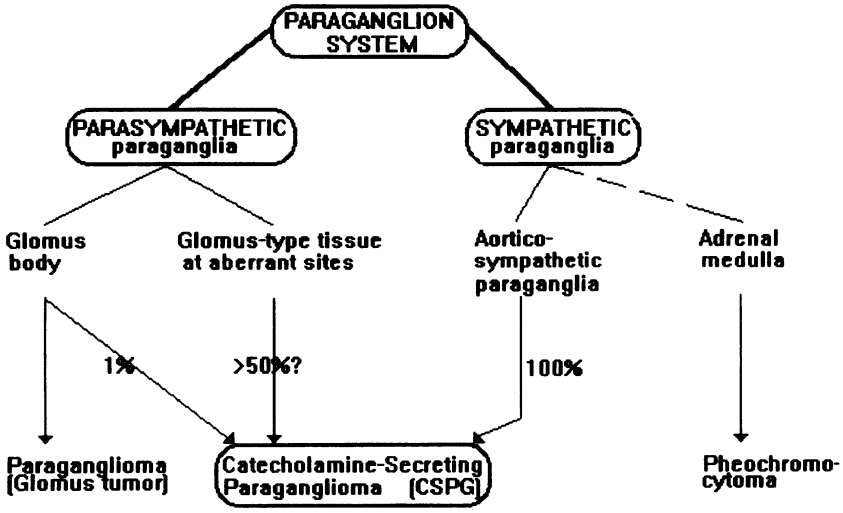

Figure 1. The paraganglion system can be subdivided into either sympathetic or parasympathetic innervation. The sympathetic paraganglia include the aorticosympathetic paraganglia and the adrenal medulla. The parasympathetic paraganglia include the glomus bodies and the aberrant glomus-type tissue. Corresponding tumors are shown at the bottom of the figure. The term paraganglioma encompasses glomus tumors and CSPG. Only 1% of glomus tumors will become active and will thus be termed CSPG, whereas the aberrant glomus-type tissue is more prone to the formation of CSPG. Pheochromocytomas will also secrete catecholamines but are not considered as paraganglioma.

reaction to dichromate staining. By far the largest sympathetic paraganglion is the adrenal medulla, although extra-adrenal chromaffin cell groups can be found along the entire sympathetic trunk in the para-aortic area. Therefore these extra-adrenal chromaffin cell groups are classified as aorticosympathetic paraganglia as proposed by Glenner and Grimley (Table 1).[2]

Glomus Bodies and the Paraganglion System

Glomus-type tissue has been reported in association with the entire parasympathetic outflow of the autonomic nervous system,[5] although most is present in close proximity to the parasympathetic nerves of the ontogenetic gill arch areas, that is, branchiomeric. This branchiomeric glomus tissue is arranged mainly in the well-known glomus bodies (for example, glomus jugulare, carotid, and aortic bodies). However, glomus-type tissue has also been found in the orbital cavity, nose and paranasal sinuses, pterygopalatine fossa, false vocal cord, cricothyroid membrane, and at other so-called aberrant sites in the head and neck region.[6–10]

There is both anatomic and ultrastructural parallelism between the glomus bodies and the sympathetic paraganglia that would suggest a common categorization. The ultrastructural appearance of their composing cells is sim-

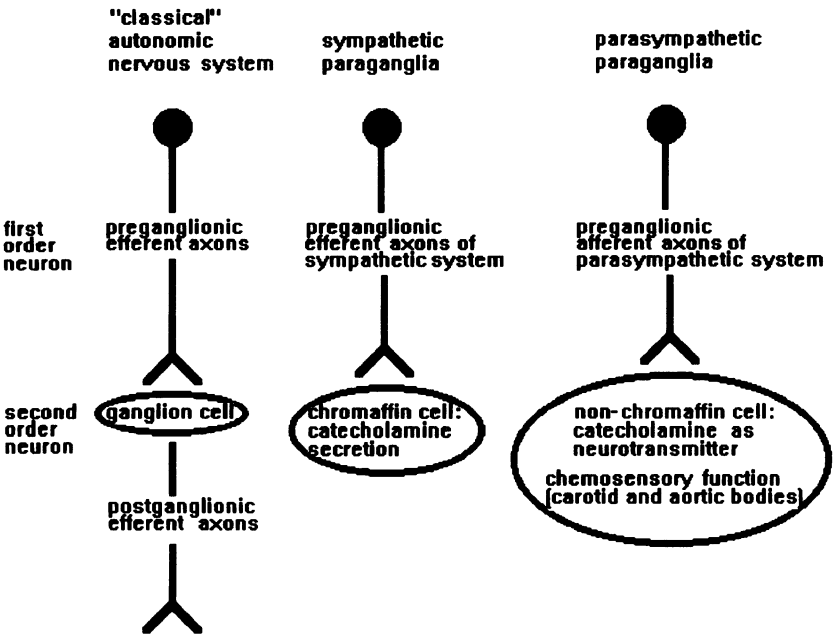

Figure 2. The peripheral pathways of the "classic" autonomic nervous system consist of first- and second-order neurons. The sympathetic and parasympathetic paraganglia are composed of modified second-order autonomic neurons. Note the differences between the sympathetic and parasympathetic paraganglia.

Table 1. Classification of Extra-Adrenal Paraganglia[2]

I.	Branchiomeric paraganglia*
	A. Jugulotympanic paraganglia related terms: glomus jugulare; glomus tympanicum
	B. Orbital paraganglia
	C. Intercarotid paraganglia related terms: carotid body or glomus caroticum
	D. Subclavian (supra-aortic) paraganglia related terms: aortic bodies
	E. Laryngeal paraganglia
	F. Aorticopulmonary paraganglia
	G. Coronary paraganglia
	H. Pulmonary paraganglia
II.	Intravagal paraganglia*
III.	Aorticosympathetic paraganglia°
IV.	Visceral-autonomic paraganglia*

* = parasympathetic paraganglia ° = sympathetic paraganglia.

ilar in that both show dense-cored secretory granules of the type known to secrete biogenic amines. It is also noted that they both lie in close proximity to major blood vessels and autonomic nerves. Therefore, these features would identify glomus bodies as parasympathetic paraganglia (Fig. 1).

However, as Gaffney pointed out,[11] there are some differences between sympathetic and parasympathetic paraganglia (Fig. 2). First, the autonomic nerves associated with the parasympathetic paraganglia are sensory parasympathetic nerves and send afferent information along to the brain stem. The carotid and aortic bodies are chemoreceptors that participate in cardiorespiratory homeostasis. Since a chemosensory function of the other glomus bodies remains to be proven,[5] using the term "chemodectoma" should be avoided. A second difference is observed when parasympathetic paraganglia are stained by the potassium dichromate method. Since the glomus bodies consistently show a negative reaction, the term *nonchromaffin* paraganglioma was introduced to denote glomus tumors. More recently, however, new techniques have clearly demonstrated that the chief cells composing the glomus bodies do store catecholamines, albeit to a lesser degree than in chromaffin cells. The secretory granules are interpreted as representing an adrenergic mechanism of synaptic transmission in parasympathetic afferent nerves. In the face of this new information, the chief cells have now gained full recognition as neuroendocrine cells[5] and as modified second-order parasympathetic neurons (Fig. 2). Accordingly, glomus tissue and bodies are now recognized as parasympathetic paraganglia. In the widely accepted classification by Glenner and Grimley, the extra-adrenal paraganglia have been grouped on the basis of ontogeny (branchiomeric), innervation (sympathetic or parasympathetic), and anatomic distribution (Table 1).[2]

Catecholamine-Secreting Paragangliomas

Since glomus bodies are now classified as paraganglia, the tumors that arise from this tissue are defined as paragangliomas (Fig. 1). In general, glomus tumors have a low production rate and release of catecholamines into the circulation. Consequently, when the glomus tumors initially failed to respond to chromaffin staining they were referred to as nonchromaffin paraganglioma. In rare instances, the secretion of catecholamines by the neoplastic chief cells of a glomus tumor will become hyperactive with a fivefold increase in the release of bioactive amines. This increase in release of catecholamines into the circulation will cause clinical symptoms which can mimic a pheochromocytoma.[12] These patients will complain of headache, excessive perspiration, palpitations, pallor, anxiety, tremor, nausea, chest or abdominal pains, and weight loss. The symptoms may come and go, with varying lengths of symptoms-free intervals following the pattern of catecholamine secretion.

When this occurs the glomus tumor is called a CSPG, or functional paraganglioma. This was first documented in 1964 by Duke et al in a glomus jugulare tumor.[13] CSPG are estimated to arise in about 1% to 2% of all glomus jugulare tumors[2–4] and have also been reported with carotid body tumors[14,15] and vagal body tumors.[16,17] In accordance with the presence of glomus-type tissue at aberrant sites in the head and neck region,[6–10] there are reports of CSPG arising in the infratemporal fossa, pterygopalatine fossa, and clivus.[7,18] Interestingly, 25% of laryngeal CSPG have malignant behavior.[15]

The CSPG also comprise the catecholamine-secreting tumors originating from the aorticosympathetic paraganglia (Fig. 1). The term pheochromocytoma should be reserved for tumors arising from the adrenal medulla.

A more general view of these types of tumors is brought together in the APUD concept. In 1968, Pearse designated as APUD cells a class of cells with widespread distribution but remarkable congruence of functional, histologic, and tumor-bearing properties.[19] The acronym APUD signifies amine precursor uptake and decarboxylation, which indicates that all APUD cells are able to decarboxylate aromatic amino acids to biogenic amines (that is, the amine hormones like the catecholamines and serotonin). Some of the most important types of cells comprising the APUD concept are listed in Table 2, as are the related tumors arising from these cells, the so-called apudomas.[20] The chief cells of glomus tissue are included in that list. All these aminergic and peptidergic endocrine cells are found to have the same kind of dense-cored granules, which are also found in neurons, thus supporting the hypothesis of a common neural crest embryologic origin. The hypothesis of a common neuroectodermal origin of the glomus body chief cells and the other APUD cells is further strengthened by the observation that some apudomas will occur simultaneously in the same patient and that neoplastic APUD cells may secrete hormones

Table 2. Examples of APUD Cells, Tumor Formed and Substance Secreted

Cells		*Apudomas*		*Substance*
1. Sympathetic paraganglia (chromaffin cells)	→	Pheochromocytoma (< adrenal medulla)	↘	
Parasympathetic paraganglia (chief cells of glomus tissue)	↗ →	CSPG	→	Catecholamines
		Paragangliomas (glomus tumor)	↗	
2. Intestinal endocrine cells	→	Carcinoid tumor	→	Serotonin
		Gastrinoma	→	Gastrine
3. Islets of Langerhans	→	Islet cell tumor	→	Insulin
4. Parafollicular C-cells	→	Medullary carcinoma of thyroid	→	Calcitonin
And others				

characteristic of other APUD cells.[20] For example, CSPG have been known to secrete calcitonin,[14,15] and carcinoid syndrome has been implicated in a glomus jugulare tumor.[21]

Case Reports

Case 1

A 38-year-old woman presented in 1975 with fluctuating hearing loss, pulsatile tinnitus, and hoarseness. She had been taking diuretics to control moderate hypertension (160/100 mm Hg) since the age of 27 and was now carrying the presumptive diagnosis of primary hyperaldosteronism for which she took spironolactone. Moreover, there was a history of several attacks of tachycardia, excessive perspiration, and anxiousness. On physical examination she had a vocal cord paralysis on the left side and there was weakness and slight atrophy of the left trapezius and sternocleidomastoid muscles. The other cranial nerves were normal. The otoscopy and audiogram were normal. The urinary catecholamines were measured as normal. Polytomography and angiography suggested a vascular tumor involving the base of the left temporal bone. Surgical exposure of the jugular bulb via a transmastoid approach failed to reveal the presence of a tumor. Three years later, in 1987, the patient re-presented with similar symptoms. This time a reddish mass was noted behind an intact left tympanic membrane, associated with a 30 dB conductive hearing loss. Computer tomography and angiography clearly demonstrated a temporal paraganglioma (C_2De_1) involving the jugular foramen and carotid canal with a large (Di_2) intradural extension. Urinary catecholamine determination was not repeated at this time. She underwent a left infratemporal fossa type A approach,[22] and the extradural portion of the tumor was removed. Intraoperatively, the blood pressure was difficult to control. The repetitive use of alpha-blockers was required to maintain a systolic blood pressure under 150 mm Hg. Persistent tachycardia was also noted during the manipulation of the tumor. Three months later the patient underwent a suboccipital craniotomy for removal of the intradural portion of the tumor. For 5 years since the resection of the CSPG the patient remained normotensive without the use of antihypertensive medications. She had a House Grade 2 facial nerve function. In 1983, the diagnosis of hyperaldosteronism was reestablished and she was put again on spironolactone. Normal urinary catecholamine levels suggested the absence of a catecholamine-secreting tumor at that time. In 1991, 13 years postexcision of the CSPG, the blood pressure was controlled by spironolactone. A urinary catecholamine determination showed normal values for vanillylmandelic acid (VMA) and norepinephrine. Repeated imaging confirmed radical tumor removal.

Case 2

A 55-year-old man presented in 1979 with hypertension and hoarseness. Despite medication, his blood pressure was 160 mm Hg systolic and 110 mm Hg diastolic. He had a decreased gag reflex, vocal cord paralysis, and tongue atrophy on the left side. The facial nerve was normal, and there were no abnormalities on otoscopy. Computer tomography, angiography, and a retrograde jugular venogram demonstrated an enhancing lesion occupying the left jugular foramen which suggested the diagnosis of a paraganglioma ($C_2De_1Di_1$). Due to the uncontrolled hypertension, preoperative urinary catecholamines were obtained (Table 3). The norepinephrine level was found to be increased. Via an infratemporal fossa type A approach the patient underwent total removal of a left temporal paraganglioma, which had an intradural extension of 1 cm. During the surgical manipulation of the tumor, the blood pressure was difficult to control, with systolic values changing abruptly between 200 and 120 mm Hg. Postoperatively, the antihypertensive medication was withdrawn gradually. Four months after surgery, urinary catecholamines had returned to normal (Table 3) and remained so for the following 12 years. Repeated imaging confirmed radical tumor removal.

Case 3

A 28-year-old female, who had bilateral glomus caroticum tumors resected at another institution at the age of the 23, presented in 1987 with a left pulsatile retromandibular mass. Despite the fact that the patient described pulse-synchronous tinnitus, no bruit was discerned on auscultation. The patient also complained of nonparoxys-

Table 3. Urinary Catecholamines and Metabolites

		VMA mg/24hr nl = 2 – 7	*NE µg/24hr nl = <60*
Case 2	preop	11	218
	postop	4	42
		VMA µmol/24hr nl = 10 – 35	NE µg/24hr nl = <80
Case 4	preop	292	5366
	postembolization	168	2366
	5 days postop	38	133
	10 days postop	53	196
		VMA µmol/24hr nl = 10 – 35	NE nmol/24hr nl = <500
Case 5	preop	220	10 370
	1 week postop	161	3608
	3 weeks postop	78	1345

Abbreviations: VMA = vanillylmandelic acid; NE = norepinephrine; nl = normal values.

mal tachycardia, excessive perspiration, and anxiousness. On physical examination, blood pressure was normal, otoscopy showed a reddish mass in the left hypotympanum under a normal tympanic membrane, and left vocal cord mobility was reduced. All other cranial nerve function was normal. Computer tomography and angiography revealed the existence of a vagal paraganglioma (glomus vagale tumor), encasing the left internal carotid artery proximal to the carotid foramen, with a C_1 intratemporal extension (Fig. 3). Urinary catecholamine determination yielded borderline increased norepinephrine values. Embolization and assessment of the contralateral blood flow were performed 1 week preoperatively. Surgery was performed via the infratemporal fossa type A approach. Radical removal of the tumor required intraoperative balloon occlusion of the internal carotid artery. Blood pressure and pulse rate were easily controlled during surgery. The postoperative course was uneventful. The patient left the hospital after 10 days. Facial function remained intact, in spite of the anterior displacement of the facial nerve. Five months later the patient underwent the removal of three abdominal catecholamine-secreting paragangliomas at another institution. A parachordal Teflon injection was successfully used to medialize the left vocal cord a year after surgery. Four years post-tumor excision she has high blood pressure (160/100 mm Hg), tachycardia (96/minute), and a slightly increased plasma norepinephrine level and urinary VMA level. Computer tomography confirmed total tumor removal (Fig. 3C, 3D).

Case 4

A 42-year-old male presented in 1984 with a 5-year history of recurrent hypertensive crises, with systolic blood pressure values up to 280 mm Hg. On admission the blood pressure was 170/120 mm Hg despite alpha- and beta-adrenergic blocking agents, and the patient showed signs of hypertensive retino- and cardiomyopathy. Blood sugar levels were elevated (180 mg%). Urinary catecholamine determination yielded extremely high norepinephrine and VMA levels (Table 3). On physical examination otoscopy was normal, and there were no deficits of the cranial nerves. Computer tomography showed a large, well-vascularized tumor in the left infratemporal fossa, destroying the middle cranial fossa base and reaching the midline at the cavernous sinus (Fig. 4A). There was destruction of the base of the left pterygoid process with invasion of the sphenoid sinus. However, the tumor remained extradural. Angiography showed the intracranial part of the tumor to be supplied by dural and cavernous branches of the internal carotid artery and the external part by the internal maxillary artery, which was embolized. Two days after the embolization, VMA and norepinephrine levels dropped by half (Table 3). Five days after the embolization, the tumor was removed in toto via an infratemporal type C approach.[22] Manipulation of the tumor gave rise to blood pressure bounding from 130/85 to 250/140 mm Hg and ventricular flutter with a pulse rate of 180/minute. Intraoperatively, after complete removal of the tumor, there was a dramatic fall in blood pressure to 50/35 mm Hg. Postoperatively, urinary catecholamine levels were only slightly elevated (Table 3), and the antihypertensive medication could be reduced. The blood sugar level returned to normal, and control computer tomography demonstrated total tumor removal. The patient remained free of disease for the following 7 years (Fig. 4B). The facial nerve is intact.

Case 5

A 23-year-old female presented in 1990 with right-sided nasal obstruction, progressive right-sided facial pain, and hypertension. Urinary catecholamines were found to be markedly elevated (Table 3). Magnetic resonance imaging showed a large, highly vascularized tumor involving the nasopharynx, sphenoid sinus, and posterior ethmoids, destroying the clivus down to the foramen magnum and involving the right cavernous sinus (Fig. 5A). During angiography, both internal maxillary arteries and the right ascending pharyngeal artery were embolized (Fig. 5C, 5D). The contralateral cerebral blood flow was good. Due to a compromised lumen of the right internal carotid artery, an occluding balloon was placed just proximal to the take-off of the right ophthalmic artery and a second balloon proximal to the carotid foramen. One week later, the patient underwent an infratemporal fossa type C approach for removal of the tumor (Fig. 5B). The tumor had destroyed the clivus and the anterior bony contour of the foramen magnum. Intraoperatively, the systolic blood pressure was maintained below 140 mm Hg with the continuous use of alpha-blocking agents. It was necessary to leave a thin sheet of infiltrating tumor to avoid entering into the subarachnoidal space at the atlanto-occipital junction. Postoperatively the antihypertensive medications were gradually withdrawn, and there has been a progressive decrease in the levels of urinary

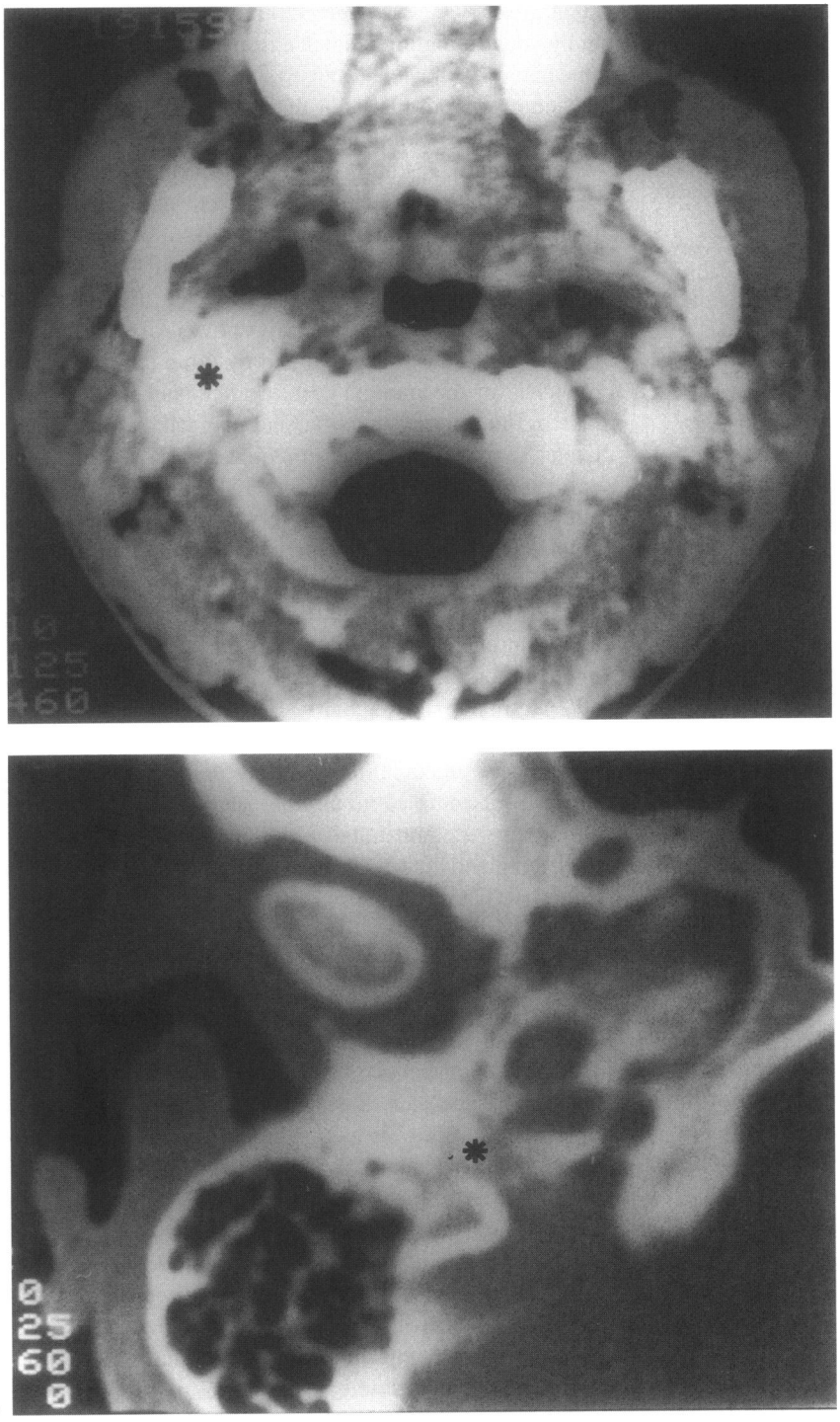

Figure 3. Vagal paraganglioma with intratemporal extension on the left side (case 3). A. Preoperative axial CT with contrast showing the tumor in the neck (✱). B. Preoperative axial CT with contrast showing the intratemporal tumor extension (✱). (Figure continued on the next page.)

catecholamines (Table 3). The patient left the hospital after 10 days with intact facial function. One year post-tumor excision, the blood pressure is slightly elevated in the morning (150/100 mm Hg), and there is a slight increase of urinary catecholamines. Imaging has shown no growth of the residual tumor.

DISCUSSION

The data of these five cases with catecholamine-secreting paraganglioma are summarized in Table 4. The patients in this series had an average age of 37, the oldest

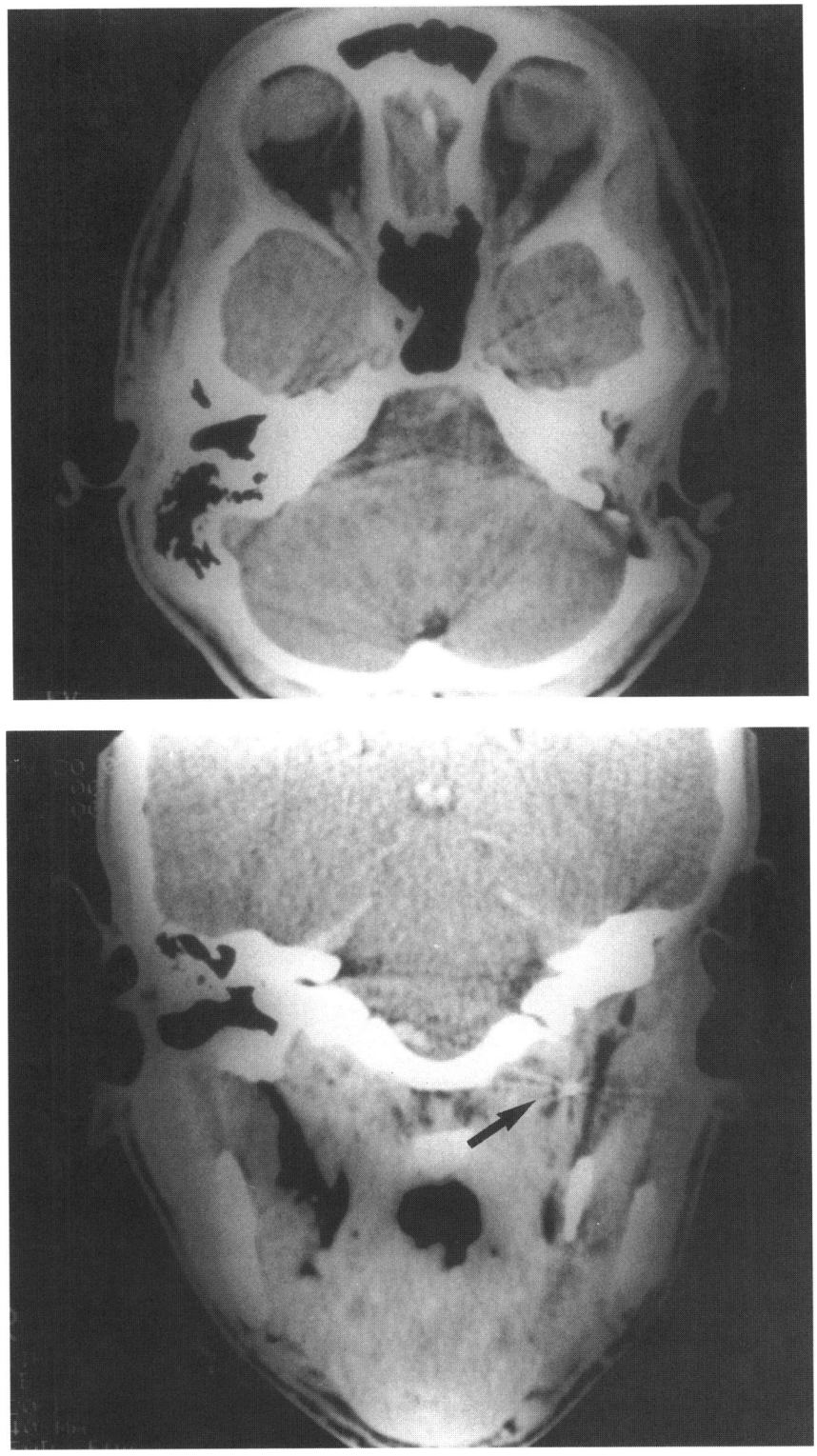

Figure 3. (Continued). C. Postoperative (3 years) axial CT showing complete tumor removal and the exenterated temporal bone. D. Postoperative (3 years) coronal CT showing complete removal of tumor and position of the proximal balloon occluding the left common carotid artery (↦).

being 55 and the youngest 23. Three out of the five patients were female. It can be generalized that CSPG tend to present earlier and larger when compared to nonsecreting glomus tumors.[21] Cases 2, 4, and 5 are clear-cut examples of norepinephrine-secreting tumors. They all show significant differences in preoperative and postoperative urinary catecholamines, all had severe hypertensive crises during surgical manipulation of the tumor, and the antihypertensive medication could be withdrawn or reduced after the intervention. Case 1 represented our first experience with a catecholamine-secreting tumor, though its identification was hampered by the simultaneous existence of primary hyperaldosteronism, which offered another explanation for the long-standing hyper-

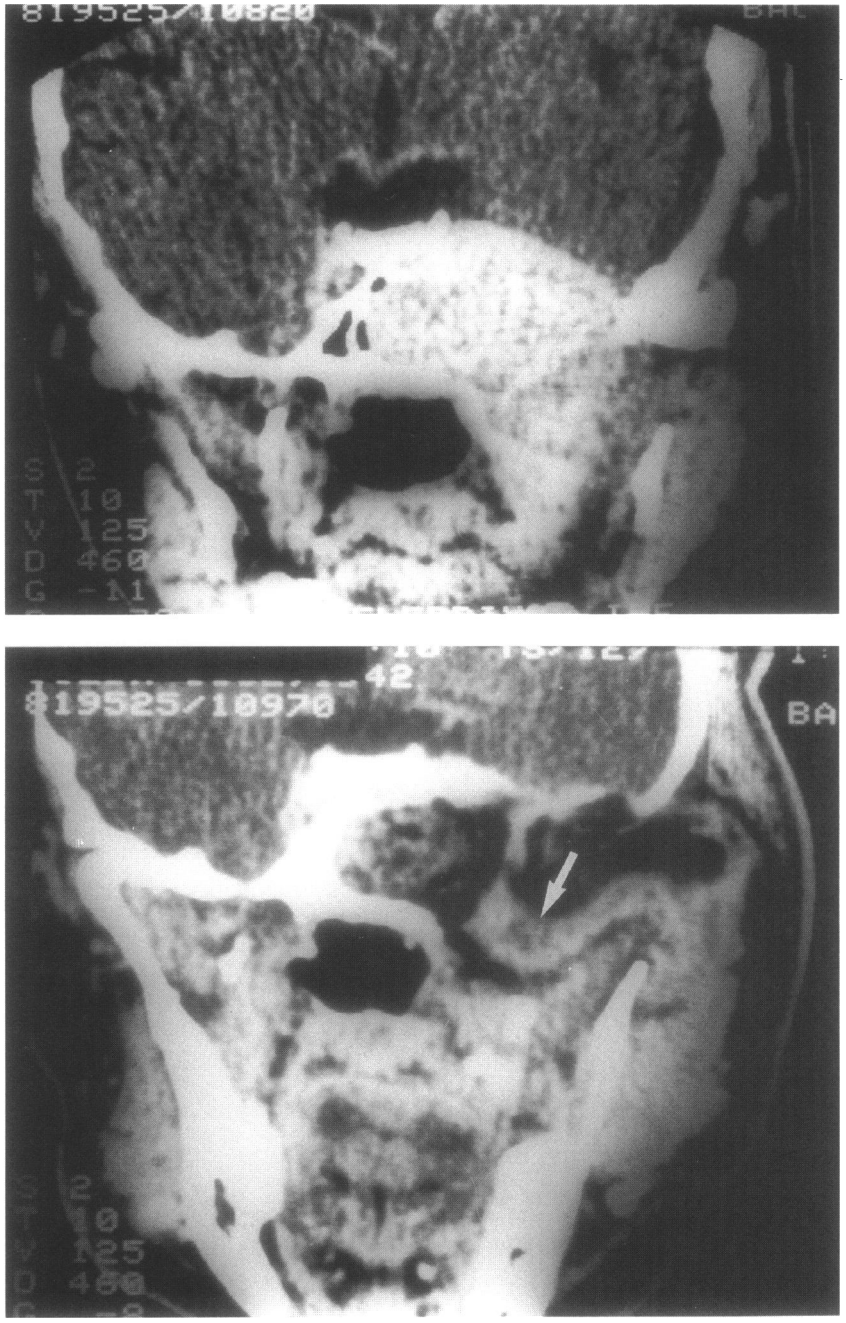

Figure 4. Infratemporal fossa paraganglioma on the left side (case 4). A. Preoperative coronal CT showing elevation of middle cranial fossa dura and invasion of sphenoid sinus. B. Postoperative (10 days) coronal CT showing radical tumor removal (infratemporal fossa approach type C) and temporalis muscle flap placed within the operative cavity (→).

tension. The persistently increased blood pressure and tachycardia with tumor dissection and the 5-year postoperative interruption of antihypertensive medication is evidence that the glomus jugulare tumor took part in the hypertensive state by secreting pressor substances. In case 3, no conclusions can be drawn on the secretory properties of the vagal paraganglioma on the basis of laboratory evaluation. This case demonstrates the possible involvement of glomus tumors (either endocrine active or silent) in a condition characterized by the presence of multiple catecholamine-secreting tumors, and thus emphasizes the importance of follow-up in glomus tumors.

The clinical picture of a patient with a CSPG mimics a pheochromocytoma, with persistent or paroxysmal hypertension according to the catecholamine release pattern. In up to half of the patients, symptoms follow the paroxysmal pattern. Thus, normal blood pressure at a single visit does not rule out a CSPG. So far as postural hypotension is a common finding, it is our recommendation that the blood pressure be measured in both supine and upright positions. As seen in case 4, hypertensive retinopathy and cardiomyopathy may be found as a result of the hyperdynamic state. Case 4 also shows elevated blood sugar levels, which is highly suggestive of increased catecholamine secretion when occurring in hypermetabolic hypertensive patients.

We recommend that when a patient complains of

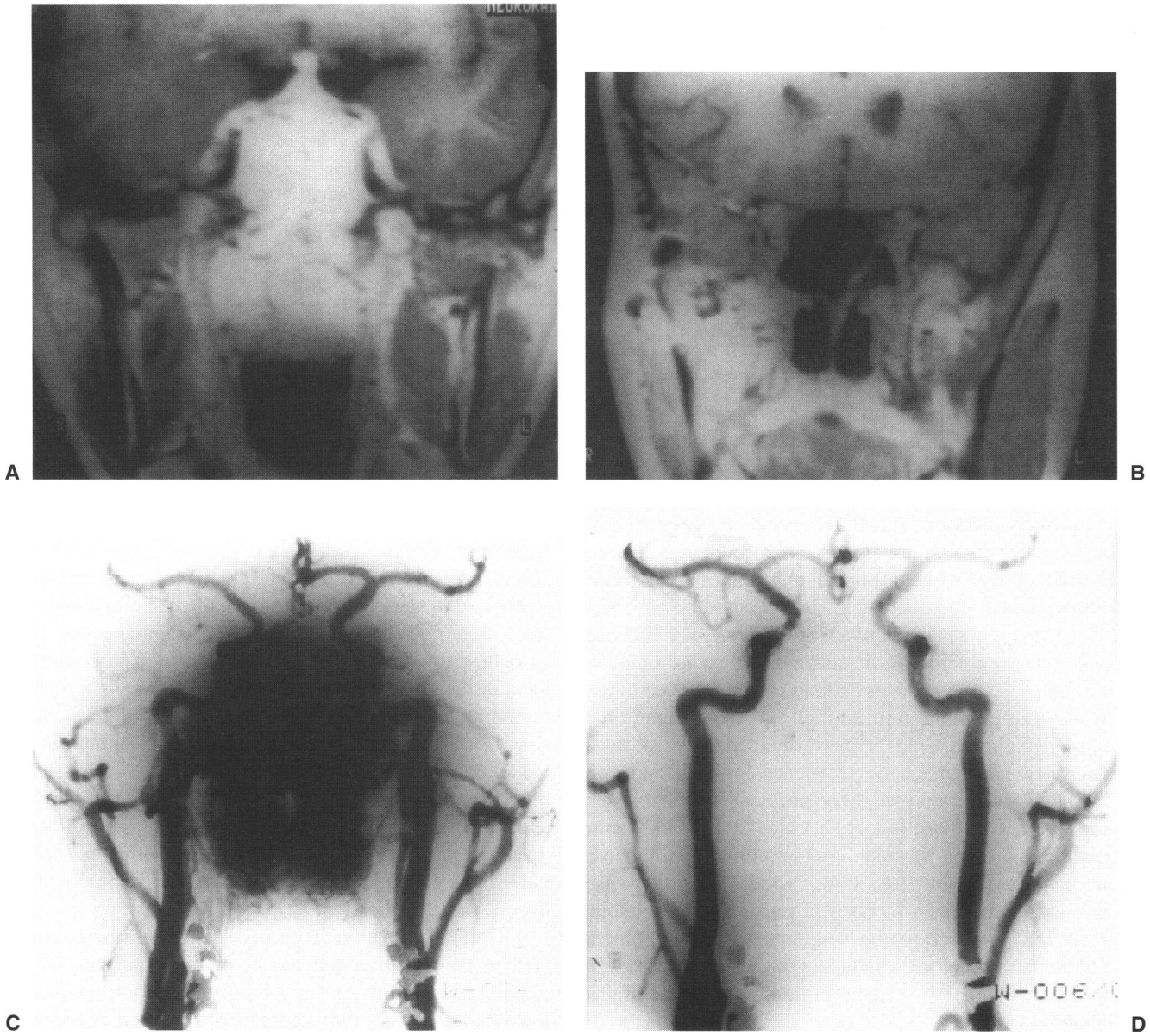

Figure 5. Nasopharyngeal paraganglioma (case 5). A. Preoperative coronal MRI showing tumor invasion of the sphenoid sinus and displacement of the right internal carotid artery close to the cavernous sinus. B. Postoperative (8 months) coronal MRI showing tumor removal and occlusion of right internal carotid artery (→). C. Preoperative angiogram showing extent of tumor. D. Angiogram after embolization.

pheochromocytoma-like symptoms, urinary catecholamines should be obtained—even in a normotensive patient. Several authors advise routine urinary catecholamine screening of all patients with glomus tumors.[16] We continue to recommend screening only those patients with hypertension or suggestive symptoms. The random screening of normotensive patients has not proved to be a useful clinical endeavor and has not uncovered any clinically silent tumors. When a CSPG of the skull base is discovered, a search should be undertaken for other CSPG throughout the body, and for pheochromocytoma.[18] A glomus tumor, either endocrine active or silent, might be involved in a condition characterized by the presence of multiple catecholamine-secreting tumors.[14,23,24] Therefore, regular follow-up with determination of urinary catecholamines on the slightest clinical suspicion is recommended. This is demonstrated by case 3, which continues to show some indications for catecholamine overproduction after removal of three abdominal CSPG. Another reason for repeated evaluation is the possibility of malignant transformation of CSPG. As in nonsecreting glomus tumors, malignancy in CSPG cannot be predicted by histologic appearance alone.[25] With metastatic spread to bone, lymph nodes, and lung, a malignant behavior of the tumor is clinically evident. CSPG may have increased malignant potential (38%) compared to pheochromocytoma (10%), and nonsecreting glomus tumors (less than 10%).[26] The malignant transformation of CSPG is partic-

Table 4. Summary of Case Reports

	Age	Location	Endocine Activity Suggested by	Multiplicity of Tumors	Substance Secreted
1	38	Glomus jugulare	Hypertension with tumor manipulation	Probably not	?
2	55	Glomus jugulare	Urinary catecholamines & hypertension with tumor manipulation	No	Norepinephrine
3	28	Vagal paraganglioma	?	Three abdominal catechol. secret. paraganglioma	Norepinephrine?
4	42	Infratemporal fossa	Urinary catecholamines & hypertension with tumor manipulation	Probably not	Norepinephrine
5	23	Nasopharynx	Urinary catecholamines & hypertension with tumor manipulation	Probaby not	Norepinephrine

ularly common for carotid and laryngeal tumors.[15] To date, none of the patients in our series have demonstrated malignant transformation. Another aspect of CSPG which would necessitate follow-up is their possible association with other endocrine (apudomas) or nonendocrine (Carney syndrome) tumors.[16,23] Carney syndrome is a recently described triad of neoplasms, consisting of gastric leiomyosarcomas, pulmonary chondrosarcomas, and CSPG.[27]

If there is suspicion of a CSPG, a venous sample for plasma norepinephrine determination can be obtained through selective catheterization near the glomus tumor. In view of possible multicentricity of these tumors, venous sampling should be performed at different sites. Comprehensive magnetic resonance imaging and conventional radiography might be necessary to localize one or more CSPG. For instance, in case 4 a total body computer tomography was required to establish the diagnosis of an infratemporal fossa tumor which did not produce any local symptoms. In cases of residual catecholamine secretion postoperatively, scintigraphy with [^{131}]metaiodobenzylguanidine, a radioisotope which is picked up by catecholamine-producing tumors, may be helpful in localization.[24]

The pharmacologic management of CSPG has been discussed extensively by Schwaber et al.[16] Despite all pharmacologic precautions, severe hypertensive crises may still occur during embolization or manipulation of the tumor. Preoperative embolization is recommended in these patients, in that it not only decreases the blood supply, but also the catecholamine production (case 4). No change in catecholamine excretion or tumor size was noted after radiation therapy in a patient with a catecholamine-secreting glomus jugulare tumor.[28]

This series of five patients presenting with a CSPG of the skull base shows that radical surgical removal is possible in the majority of cases. The first two cases concerned glomus jugulare tumors. No embolization was available at that time. Total removal was accomplished via an infratemporal type A approach[22] (in combination with a craniotomy for removal of the intradural portion in case 1). Thirteen years clinical follow-up in case 1, and normal postoperative urinary catecholamine determination in case 2, respectively, indicate total tumor removal. The resection of the vagal paraganglioma in case 3 required intraoperative balloon occlusion of the internal carotid artery, with resection of both the internal and external carotid artery. In cases 4 and 5, the CSPG presented closer to the midline of the skull base, and both were managed via an infratemporal type C approach.[22] In case 4, embolization of the internal maxillary artery was performed 1 week before removal of the infratemporal fossa tumor, which was complete as demonstrated by computed tomography up to 7 years later. The involvement of the internal carotid artery by the nasopharyngeal tumor in case 5 necessitated a preoperative balloon occlusion. One week later subtotal removal was accomplished via an infratemporal fossa type C approach. A thin sheet of infiltrating tumor was left in the area of the clivus to avoid entering into the subarachnoidal space. The follow-up (1 year) is too short to establish the fate of the residual tumor. The patient is, however, fully active without antihypertensive medication.

Glomus-type tissue at so-called aberrant sites is situated in the more medial aspect of the head and neck region, as opposed to the well-known glomus bodies found in the region of the temporal bone. Paragangliomas that arise from glomus-type tissue closer to the midline of the skull base seem to be more prone to the formation of active biogenic amines (Fig. 1). This assumption is inferred both from the literature review and from our own patient population in whom we are not aware of paraganglioma at the medial aspect of the skull base that was not secreting catecholamines. The exact origin of CSPG arising in the infratemporal fossa and the nasopharynx remains speculative. As discussed above, glomus-type tissue (that is, parasympathetic paraganglia) is found in close proximity to both parasympathetic nerves and major blood vessels. Girgis and Fahmy have shown that paraganglionic tissue is normally present at birth surrounding the terminal part of the internal maxillary artery in the pterygopalatine fossa.[29] They suggested that both juvenile angiofibromas and CSPG of the nasopharynx have their origin in this tissue. Previous reports describing CSPG of the clivus, pterygopalatine fossa, and infratemporal fossa offer no explanation.[7,18] One report attributed the site of origin of two nonsecreting paragangliomas of

the nasopharynx to the nodose ganglion of the vagus nerve.[10] Within the pterygopalatine and infratemporal fossa, paraganglionic tissue, related to the pterygopalatine and otic ganglion, respectively, is adjacent to the maxillary artery. We believe this association explains the occurrence of CSPG in the nasopharynx and infratemporal fossa.

CONCLUSIONS

The previous attempts to clarify glomus tumors as nonchromaffin tumors are based on an antiquated laboratory test and should be abandoned. The accepted nomenclature considers glomus tumors to belong to the parasympathetic arm of a family of paraganglia tumors. This explains why they sometimes secrete a large amount of catecholamines into the circulation. Paragangliomas that arise from the glomus-type tissue close to the midline of the skull base seem to be more prone to be metabolically active than those arising from the glomus bodies that are found in the region of the temporal bone. CSPG will present with signs and symptoms of a hyperdynamic state, mimicking a pheochromocytoma. We recommend screening the urine for abnormally high levels of biogenic amines in those patients who are found to have hypertension in the preoperative work-up or who have symptoms suggestive of a hyperdynamic state. There should be close follow-up for patients who have had a CSPG, both for malignancy and for the formation of further catecholamine-secreting tumors, as well as other endocrine or nonendocrine tumors. As shown in this series of five patients, radical removal is possible if the appropriate approach and surgical techniques are used.

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