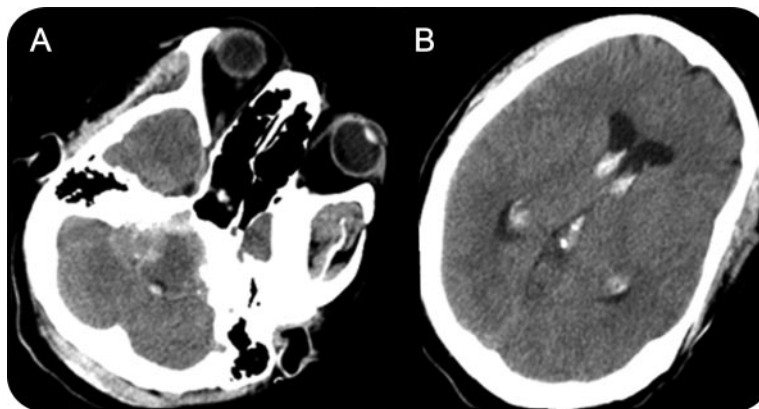


Clinical Reasoning: A rare cause of subarachnoid hemorrhage

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Figure 1 Initial head CT scan revealing subarachnoid hemorrhage



(A) Noncontrast brain CT scan demonstrates a posterior fossa mass and subarachnoid hemorrhage. (B) Intraventricular hemorrhage is also demonstrated.

SECTION 1

A 48-year-old woman presented with severe headache radiating to her neck and chest, followed by a brief period of loss of consciousness in the emergency department. After she regained consciousness, the patient described a 2-year history of right-sided pulsatile tinnitus and hearing loss. She also had a history of poorly controlled hypertension and of noncompliance with her medication. On examination her blood

pressure was 239/90 mm Hg. Results of a neurologic examination were unremarkable. Brain CT showed a subarachnoid hemorrhage (figure 1, A and B).

Questions for consideration:

1. What are the possible etiologies of her subarachnoid hemorrhage?
2. What additional diagnostic testing would you consider at this point?

GO TO SECTION 2

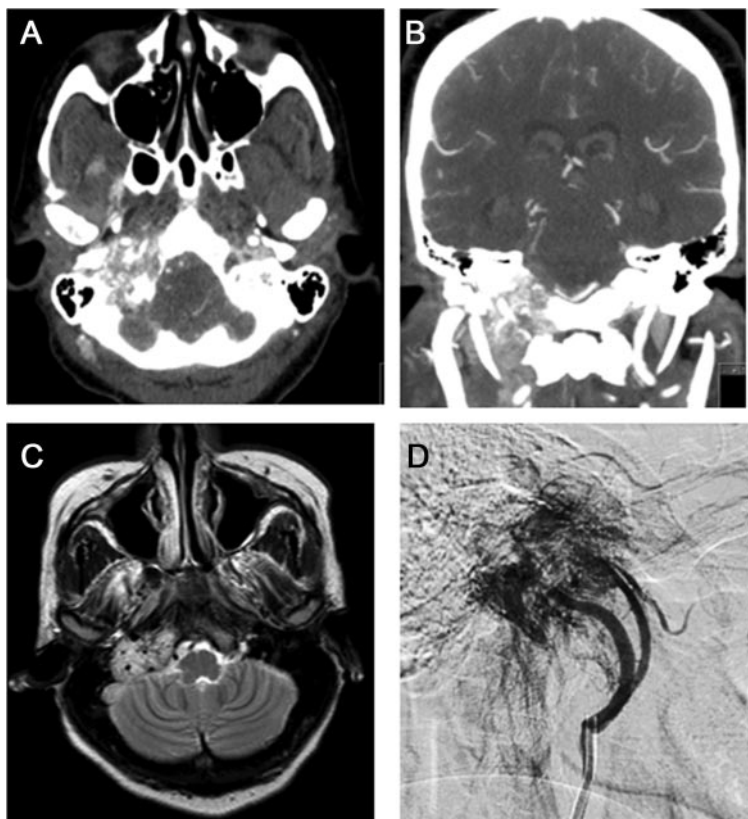
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See page e46 for mystery case responses.

Figure 2 Radiologic imaging study revealing a jugular foramen mass



(A) CT angiogram showing an enhancing jugular foramen mass extending into the posterior fossa. (B) Enhancing tumor mass at the skull base. (C) MRI T2-weighted image showed salt-and-pepper appearance. (D) Selective right ascending pharyngeal angiogram lateral view shows a hypervascularized tumor blush, fed by 2 major branches from the enlarged right ascending pharyngeal artery.

SECTION 2

CT angiography of the head and neck did not reveal any intracranial aneurysm or vascular malformation (figure 2, A and B). However, a large mass was present in the right jugular foramen with erosion of temporal bone and encroachment of the right internal acoustic canal. MRI confirmed a hypervascular mass that contained numerous flow voids. The mass was located lateral to the medulla and extended superiorly into the cerebellopontine angle cistern. It extended inferiorly to the superior aspect of the right parapharyngeal space and displaced the right internal carotid artery (figure 2C).

Catheter-based cerebral angiography demonstrated an intense hypervascular tumor blush extending from the superior aspect of the right carotid sheath into the skull base (figure 2D). The major feeding arteries were from branches of the right internal maxillary artery, ascending pharyngeal artery, and posterior auricular artery. Ear, nose, and throat evaluation revealed a reddish mass in the middle ear visible through the tympanic membrane and right vocal cord paresis with minimal abduction. The patient denied any hoarseness, dysphagia, dysarthria, or focal neurologic deficits.

Questions for consideration:

1. What is your differential diagnosis at this point?
2. How would you manage this patient?

GO TO SECTION 3

SECTION 3

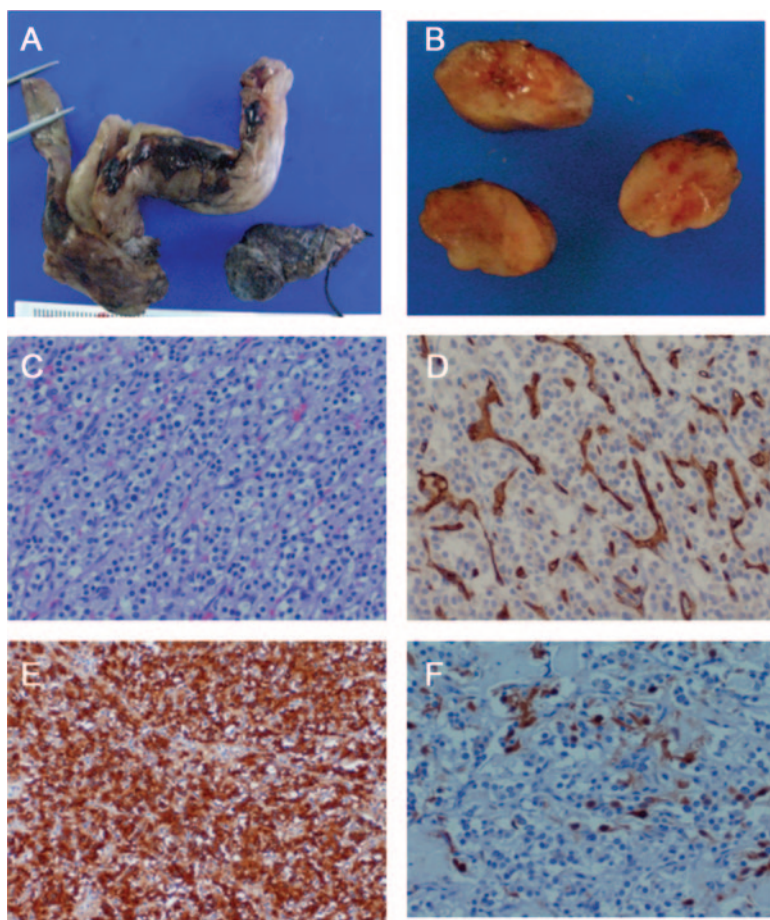
A 24-hour urine sample demonstrated elevated metanephrine (1,519 $\mu\text{g}/24$ h; reference, 95–475 $\mu\text{g}/24$ h) and normetanephrine (567 $\mu\text{g}/24$ h; reference, 52–310 $\mu\text{g}/24$ h) levels but normal urinary vanillylmandelic acid. There was no adrenal mass on abdominal MRI. The patient's hypertension was treated with phenoxybenzamine, nicardipine, metoprolol, and hydralazine.

After preoperative embolization of the right external carotid artery feeders, the patient underwent tumor removal by a transpetrosal/infratemporal fossa approach. A large red mass was seen within the middle ear space with substantial extension through the skull base and intracranially. The tumor extended through the jugular foramen, and there was considerable erosion of the petrous apex of the temporal bone. The intracranial tumor abutted the lateral portion of the lower pons and medulla. There were several large arterial feeders from the anterior inferior

cerebellar artery. The internal jugular vein was massively distended with tumor extending several centimeters inferiorly inside the lumen of the vein. This portion of the tumor was removed en bloc and measured 8.0 cm by 1.7 cm by 0.8 cm. It was a sausage-shaped hemorrhagic tumor with gelatinous appearance, which on cut surface examination had a homogeneous tan pinkish appearance (figure 3, A and B). The remainder of the tumor was removed in a piecemeal fashion. Access to the tumor required rerouting of the facial nerve. The tumor displaced the nearby glossopharyngeal, vagus, spinal accessory, and hypoglossal nerves.

Microscopically, the tumor was very vascular (figure 3, C and D). The vessels within the tumor separated the cells into irregular groups causing a zellballen pattern (figure 3, C and D). The vessels were distinctly stained by CD34 (figure 3D). The chief cells were positive by chromogranin (figure 3E) and synaptophysin (not shown). The sustentacular cells were positive by S100 (figure 3F). The anatomic diagnosis was jugulotympanic paraganglioma. Immediately after surgery, her tinnitus resolved. The patient developed new facial weakness from rerouting of the facial nerve, which continues to improve. Her hypertension has also improved but has not completely resolved.

Figure 3 Resection specimens revealing paraganglioma



(A, B) Portion of the mass from inside the lumen of the jugular vein revealed a tumor, 8 cm \times 1.7 cm \times 0.8 cm, with a tan pinkish cut surface. A photomicrograph of the mass (C, hematoxylin & eosin) reveals a highly vascularized tumor with nests of tumor cells (zellballen) separated by small blood vessels. (D) CD34 stain highlights the vessels. (E) Diffuse chromogranin immunoreactivity. (F) Scattered S100-positive cells (sustentacular cells) are seen.

DISCUSSION A paraganglioma is a very unusual cause of subarachnoid hemorrhage. To our knowledge, this is the second case reported in the literature.¹ Paragangliomas, also known as chemodectomas or glomus tumors, are rare tumors derived from the extra-adrenal paraganglionic tissue that is thought to originate from the neural crest.² They are biologically similar to pheochromocytomas. It has been estimated that paragangliomas comprise 1 in 30,000 of all head and neck tumors. Paragangliomas of the head and neck are seen in 4 primary locations: the jugular bulb, the middle ear cavity, the vagus nerve, and the carotid body. The most common paraganglioma of the head and neck is the carotid body tumor, followed by jugulotympanic paragangliomas (glomus tympanicum and glomus jugulare) and then by vagal paragangliomas (glomus vagale).² Glomus tympanicum is the most common neoplasm of the middle ear and arises from the paraganglionic tissue in the cochlear promontory. Glomus jugulare tumors arise from paraganglionic tissue along the jugular bulb adventitia. When their origin to the promontory cannot be ascertained, they are called jugulotympanic paragangliomas.³

Histologically, paraganglia contain 2 cell types: chief cells and supporting sustentacular cells. These

are characteristically arranged in “cell balls” (zellballen) surrounded by a prominent capillary network. Chief cells contain dense-core granules filled with catecholamines.³ By immunohistochemical analysis, the chief cells stain with markers of neural differentiation, including synaptophysin, neuron-specific enolase, and chromogranin.⁴ Sustentacular cells stain with S100 and focally with glial fibrillary acidic protein. Their function is not entirely clear.²

Paragangliomas are considered benign but can cause extensive destruction by their unrestrained growth. Patients with glomus tympanicum and glomus jugulare often present with similar clinical features such as pulsatile tinnitus and hearing loss, which are related to the growth of this very vascular tumor within the middle ear space. At later stages, lower cranial neuropathies (glossopharyngeal, vagus, and accessory nerves) are also common.⁵ Clinically significant hormone secretion is present in only 2% of patients. Signs suggestive of hormonally active tumor (e.g., labile hypertension, facial flushing, and tachycardia) mandate a thorough evaluation to rule out pheochromocytoma.³ Symptoms of intracranial extension are often subtle unless the tumor is large enough to cause brainstem compression or hydrocephalus. Subarachnoid hemorrhage as a presenting symptom is very uncommon but not surprising, given the highly vascular nature of these lesions and their frequent association with hypertension.

CT imaging is excellent for demonstrating characteristic bony destructive skull base changes. MRI is superior for evaluating tumor vascularity and extension. On T1-weighted images paragangliomas appear hypointense with a speckled appearance. On gadolinium-enhanced T1 images, early and pronounced enhancement is seen, witnessing the hypervascular nature of the neoplasm. The serpentine flow void pattern, described as “salt-and-pepper” appearance, is characteristic of these tumors.³ Neuroimaging may permit differentiation of paragangliomas from 2 other common jugular foramen lesions, meningioma and schwannoma. Primary jugular foramen meningiomas are characterized by a permeative sclerotic appearance of the bone margins of the jugular foramen and the presence of dural tails. Schwannomas cause expansion of the jugular foramen with scalloped well-corticated bone margins, without skull base infiltration.⁶

The management of paragangliomas is challenging because of their hypervascular nature, advanced stage at diagnosis, and difficult anatomic location. Surgery remains the mainstay of treatment for young healthy patients with functional cranial nerve deficits. Radiotherapy or stereotactic radiosurgery can be used as an adjunct to surgery and as a primary treat-

ment modality in patients who are poor surgical candidates or those with bilateral disease.³

DISCLOSURE

Dr. Emami, Dr. Panichpisal, Dr. Benardete, Dr. Hanson, Dr. Mangla, and Dr. Rao report no disclosures. Dr. Baird serves on the editorial boards of *Stroke* and *Stroke Research and Treatment*; has received intramural and extramural funding from the NIH; is primary inventor of a patent re: The differential expression of molecules associated with acute stroke and pending patents re: The differential expression of molecules associated with vascular disease risk and intracerebral hemorrhage; has served as a consultant for Avanir Pharmaceuticals; and has received funding for travel and speaker honoraria from for Avanir Pharmaceuticals and Mitsubishi Tanabe Pharma Corporation.

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MYSTERY CASE RESPONSES The Mystery Case series was developed by the *Neurology*[®] Resident & Fellow Section to develop trainees’ clinical reasoning skills. Residency programs, medical student preceptors, and individuals were invited to use this Mystery Case as an education tool. The responses were solicited through group e-mail and through social media including Facebook and Twitter. Groups or individuals read the case presentation, developed their own differential diagnoses, and determined what diagnostic testing should be preformed.

There were 16 responses to this Mystery Case, 2 of which were submitted via social media. All but one of the submissions were from individuals. All were well-reasoned and thoughtful, and many were detailed, including extensive discussions of the differential and possible testing and treatment options.

The majority of the respondents considered the patient’s history of tinnitus and intermittent hypertension. The most common diagnosis suggested was the correct diagnosis of paraganglioma, suggested by

50% of respondents. Additional considerations, in descending order of the number of times that they were cited, included arteriovenous malformation, cerebellopontine angle tumor, carotid dissection, congenital malformation, and reversible cerebral vasoconstriction syndrome.

The most frequently recommended diagnostic test was angiography (54% of respondents). The other recommendations in descending order of the number of times that they were cited included

MRI with contrast, 24-hour urine collection for catecholamine metabolites, otoscopy, and CT of the chest, abdomen, and pelvis.

This is the third Mystery Case published in the Resident & Fellow section of *Neurology*[®]. This case demonstrates the importance of multimodality imaging and attention to systemic symptoms, which may aid the practitioner in making the correct diagnosis.

Keith R. Ridel, MD

Neurology[®]

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