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CLINICAL CASE SEMINAR

Greetings from Below the Aortic Arch! The Paradigm of Cardiac Paraganglioma

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A 42-yr-old female, mother of five children, was referred to this institution for further evaluation of recurrent episodes of severe arterial hypertension. Blood pressures taken on several occasions during the past 3 yr by her general practitioner had documented recurrent hypertensive crises with systolic/diastolic measurements of up to 300/145 mm Hg. These episodes were frequently accompanied by headache, palpitations, sweating, nausea, and pallor followed by weakness. Her past medical history was remarkable only for transient hepatitis B following blood transfusion in 1970 and Cesarian section in 1986. Family history was negative for multiple endocrine neoplasia (MEN) type 2A and 2B syndromes, von Recklinghausen's neurofibromatosis, and von Hippel-Lindau's disease. Her medications included intermittent usage of furosemide (40 mg/day) for leg edema and L-thyroxine (200 μg/day) for a history of hypothyroidism. Diagnostic tests before referral had revealed an elevated 24-h urinary excretion of vanillylmandelic acid at 27 mg/24 h (0.3–7.7 mg/24 h) and normal 24-h urinary excretion of catecholamines. In addition, on computed tomography of the abdomen, a right adrenal mass had been detected. Physical examination revealed moderate obesity (170 cm, 83 kg) and marked hypertension (180/115 to 230/120 mm Hg) but was otherwise normal. No heart murmurs were heard, and fundoscopic and skin examination were unremarkable. Twenty-four hour blood pressure monitoring demonstrated a systolic mean of 170 mm Hg without diurnal rhythm.

Serum electrolytes were normal except for mildly elevated corrected calcium levels of 2.6–2.8 mmol/L (2.0–2.5 mmol/L) and a low potassium level of 3.3 mmol/L (3.5–5.5 mmol/L). All other routine blood tests were within normal limits. Total 24-h urinary catecholamine measurements revealed markedly elevated concentrations of norepinephrine at 912 μg/24 h (<100 μg/24 h), metanephrines at 4.5 mg/24 h (<1.3 mg/24 h), and vanillylmandelic acid at 18 mg/24 h (<8 mg/24 h), whereas epinephrine and dopamine concentrations were normal. Thyroid function tests revealed complete suppression of basal TSH at <0.03 mU/L (0.4–4.0 mU/L), elevated free T_4 concentration of 2.3 μg/L (0.8–1.8 μg/L), normal free T_3 concentration, and normal thyroglobulin and thyroid peroxidase autoantibody titers. Intact PTH level was markedly elevated at 160 ng/L (10–55 ng/L). Measurements of pituitary hormones, calcitonin and carcinoembryonic antigen were all within normal limits. Thyroid hormone medication was discontinued, and antihypertensive treatment was started with phenoxybenzamine and titrated to 40 mg/day until satisfactory control of blood pressure was achieved. A roentgenogram of the thorax was normal. ECG registration revealed normal sinus rhythmus at 60/min and was normal except for a slow R-wave progression in the anterior leads. Transthoracic echocardiography demonstrated left ventricular diameters at the upper range of normal and moderate mitral valve insufficiency. Magnetic resonance imaging (MRI) of the adrenal glands confirmed the presence of a 1.5 × 2.5 cm right adrenal mass which, on T_2-weighted images, failed to reveal high signal intensity. In search for a catecholamine-producing tumor at an extraadrenal site, ^{131}I-meta-iodobenzylguanidine (MIBG) whole body imaging was performed and revealed significant uptake medially in the mediastinum at the level of the 6th vertebral body (Fig. 1). A CT scan of the mediastinum localized a well-demarcated mass of 5 cm in diameter adjacent to the carina without obvious infiltration into neighboring structures. ECG-triggered MRI of the mediastinum located the mass on top of the left atrium and just below the carina. High signal intensity of this mass was demonstrated on T_2-weighted MRI images (Fig. 2). No evidence of a parathyroid tumor was found on MRI studies extended to the neck and upper mediastinal area. Transesophageal echocardiography (TEE) demonstrated the mediastinal mass to be well-defined and situated on top of the pulmonary artery bifurcation just below the aortic arch (Fig. 3). On coronary angiography, blood supply of the mass was found to originate from both the circumflex and the right coronary artery. Cardiac paraganglioma coexisting with a right adrenal gland incidentaloma and PTH-mediated hypercalcemia were diagnosed, and the patient was prepared for removal of the cardiac paraganglioma.

Clinical Course

Preoperatively, vigorous loading with iv fluids and phenoxybenzamine (up to 200 mg/day) was continued until signs of orthostasis occurred, whereas blood pressure was

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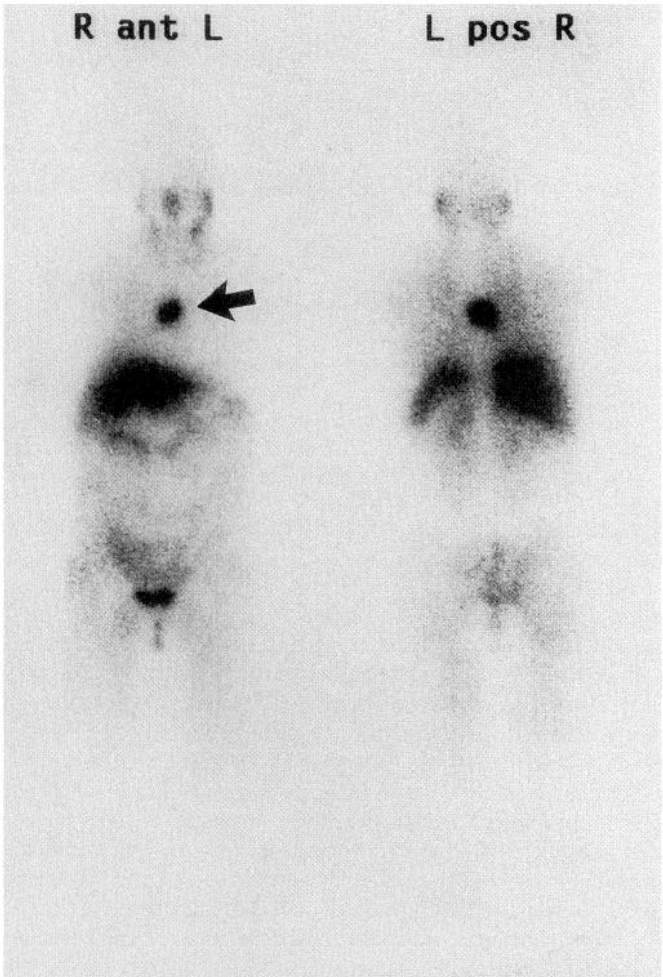

FIG. 1. ^{131}I-MIBG whole body imaging demonstrates strong radionuclide uptake in the mediastinum (*arrow*).

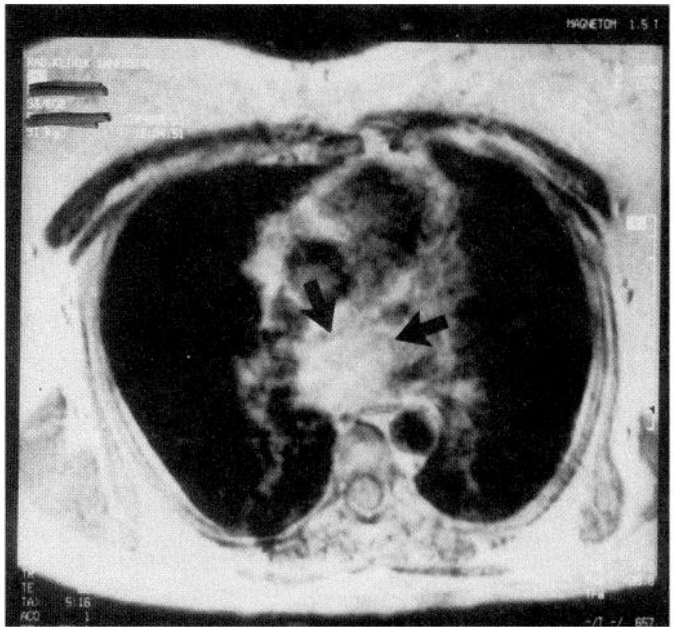

FIG. 2. MRI images (T_2-weighted) of the mediastinal mass (*arrows*) demonstrated in Fig. 1. High signal intensity of the mass is consistent with an extraadrenal pheochromocytoma.

well controlled at 140/90 mm Hg. At surgery, the mass was found to infiltrate the left atrium from above and to require transsection of the ascending aorta and pulmonary artery with cardiopulmonary bypass for proper surgical exposure and tumor removal. The mass was totally resected, and atrioplasty was performed using a pericardial patch. Histopathology revealed a highly vascularized tumor containing large polygonal chromaffin cells within a connective tissue capsule consistent with cardiac paraganglioma. The intra- and postoperative course was uncomplicated, and postoperative blood pressure measurements and catecholamine excretion returned to normal. Postoperative thyroid function tests were normal. In addition, serum concentrations for intact PTH had dropped to normal levels on repeated measurements, and corrected serum calcium concentrations fell to high normal levels (2.5–2.6 mmol/L). Pentagastrin-stimulated calcitonin levels were within normal limits. On follow-up visit 2 yr later, the patient felt entirely well, and her blood pressure measurements continued to be normal. Urinary catecholamine and metanephrine concentrations were normal, as were serum calcium and intact PTH levels. Pentagastrin-stimulated calcitonin levels were again within normal limits. A CT scan confirmed that the size of the right adrenal mass had remained unchanged.

Discussion

Location of extraadrenal pheochromocytoma may be highly variable, ranging from the pelvic floor up to the carotid bodies. Extraabdominal location of pheochromocytoma is a rare clinical entity accounting for only 3% of all cases. Two thirds of these tumors are located in the thorax and the remainder in the neck region (1). The view that these tumors are more frequently malignant has been abandoned. However, unusual clinical features frequently occur in patients with extraadrenal tumors and may include a mediastinal mass, upper airway obstruction, or gross hematuria and micturition-associated hypertensive crisis due to a tumor located in the bladder. Less than 50 cases of paragangliomas affecting the heart have been reported to date (2–4). Due to improved diagnostic localization techniques, cardiac pheochromocytomas are detected with increasing frequency. These tumors are predominantly located in close proximity to the atrial structures, affecting the left atrium more commonly than the right (4). Cardiac paragangliomas are thought to mainly arise from chromaffin cells adjacent to cardiac sympathetic fibers, or to be of ectopic origin (3). Early diagnosis and precise localization are mandatory because complete surgical resection may be curative in the majority of cases (4). However, in many instances, appropriate surgical management of cardiac paraganglioma may be only achieved with full thickness excision of the atrial wall requiring cardiopulmonary bypass, followed by atrial reconstruction using a pericardial patch (4). Intraoperative transsection of the great vessels, coronary artery bypass, and even cardiac autotransplantation may be required in rare instances where excision would otherwise remain incomplete

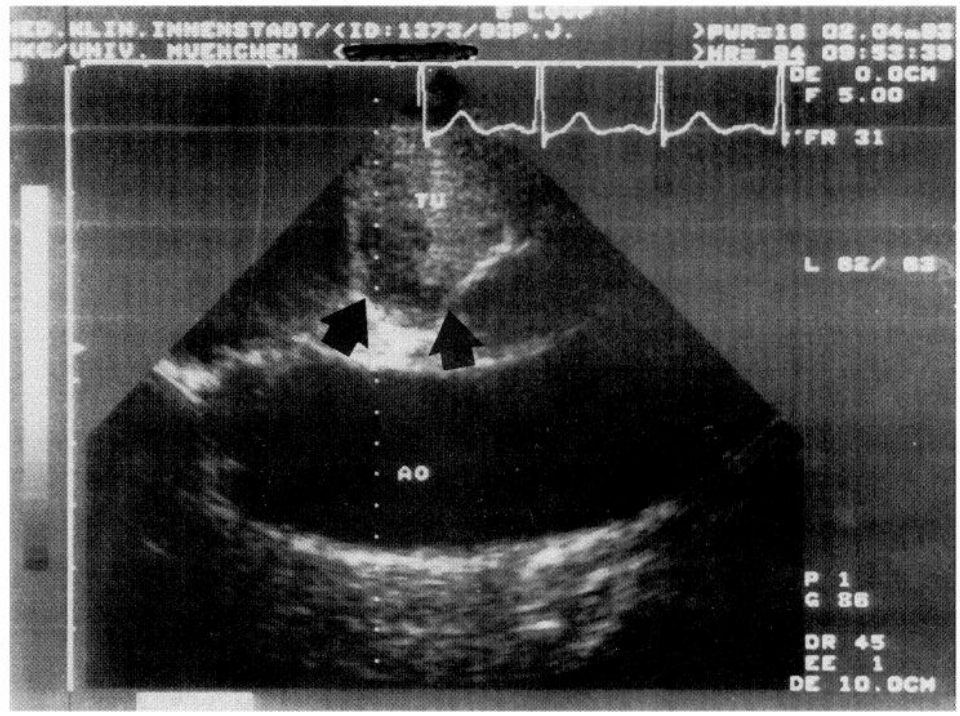

FIG. 3. TEE demonstrates the location of the tumor (*arrows*) between the ascending and descending aorta and adjacent to the pulmonary artery and the left cardiac auricle.

(2–4). As demonstrated here, administration of incremental high doses of an α-adrenoreceptor blocking agent and generous replacement of increased plasma volume requirements throughout the perioperative period may be essential to assure a good clinical outcome in these patients.

The presence of the clinical triad of headache, sweating and palpitations in a hypertensive individual is considered to be highly predictive of pheochromocytoma (1). In addition to clearcut biochemical evidence of a catecholamine-producing tumor, all of these features were present in our patient. Thus, localization rather than diagnosis was the challenge. Although the adrenal mass revealed by the outside CT scan was suspicious for an intraadrenal pheochromocytoma, there were also some hints in favor of an extraadrenal tumor location. First, biochemical testing revealed elevated norepinephrine levels but normal epinephrine levels. Although a majority of pheochromocytomas predominantly release norepinephrine, intraadrenal pheochromocytomas frequently also produce elevated levels of epinephrine. In fact, tumors that secrete only epinephrine tend to be familial and intraadrenal in origin (1). Rarely, tumors may secrete dopamine, which does not cause hypertension but may be a clue to malignant pheochromocytoma (1). However, definitive diagnosis of malignancy is still based on the finding of direct invasion or distant metastases and cannot be established on the basis of clinical, biochemical, or histologic criteria. Biochemical testing succeeds to establish the diagnosis in over 95% of cases and largely depends on tumor size or activity, or both, but not on its location (1). It has been suggested that urinary norepinephrine excretion over 156 μg/24 h, urinary vanillylmandelic acid excretion over 11 mg/24 h, urinary total metanephrine excretion over 1.8 μg/24 h, or a sum of resting norepinephrine and epinephrine plasma levels of more than 2000 ng/L are diagnostic of pheochromocytoma (1, 5). Sensitivities of elevated urinary and plasma levels of catecholamines or urinary metanephrine levels appear to be superior to that of vanillylmandelic acid excretion. For unknown reasons, sensitivity of biochemical tests in patients with pheochromocytomas occurring in the context of MEN 2A are substantially lower, ranging from 86% for urinary norepinephrine levels to only 33% for plasma epinephrine levels (1). In addition, chromogranin A serum levels may be a complementary diagnostic tool in patients with normal creatinine clearance, especially because drugs commonly used to treat patients with pheochromocytoma do not interfere with its activity or detection (1). However, diagnostic specificity of this parameter approximates only 50% in patients with a creatinine clearance of less than 80 mL/min. If biochemical tests fail to unequivocally establish a diagnosis of pheochromocytoma and clinical suspicion persists, additional dynamic tests such as clonidine suppression test may be required to discriminate between pheochromocytoma and other conditions causing increased sympathetic activity (1).

A second clue to an extraadrenal location of the catecholamine-producing tumor came from MRI studies of the adrenal glands. These studies confirmed the presence and location of the mass previously detected on the outside CT scan but demonstrated low signal intensity of this tumor on T_2-weighted images, a finding not usually consistent with pheochromocytoma. Diagnosis of pheochromocytoma rests with the presence of characteristic clinical signs and symptoms and biochemical proof of excessive catecholamine production, followed by localization of its source. In the presence of suggestive clinical and biochemical features, localization of an adrenal mass by computed tomography is usually straightforward. However, this widely used diagnostic strategy cannot differentiate between adrenal pheochromocytoma and incidentaloma. Although of little rele-

vance to the usual patient with pheochromocytoma, this strategy may be potentially catastrophic in the rare instance where a nonfunctioning adrenal mass happens to coincide with, and in fact, conceals an extraadrenal catecholamine-producing tumor. As demonstrated in this report, omission of additional imaging studies using either MRI imaging or MIBG scanning might not only have placed our patient at high risk for serious complications during surgical removal of her adrenal incidentaloma, but, in addition, would have subjected her to unnecessary surgery that left her actual problem untouched.

Despite progress in imaging techniques, localization and treatment of paragangliomas has remained a challenge. Following biochemical confirmation of suspected pheochromocytoma, a stepwise localization procedure should be followed for preoperative localization of the tumor site. Although CT and MRI appear to have similar sensitivities in localizing pheochromocytomas (98% and 100%, respectively), specificities are substantially lower at 70% and 67%, respectively (1). In patients with increased catecholamine or catecholamine metabolite excretion and normal appearing adrenal glands on CT or MRI scans, the possibility of extraadrenal pheochromocytoma must be considered. Lesions within the chest may be visible by chest radiography and are usually obvious on CT scans. As a general *caveat*, CT scanning with iv contrast enhancement should be performed only after appropriate α- and β-adrenoreceptorblockade for prevention of hypertensive crisis (1, 5). The usefulness of CT or MRI scans in localizing extraadrenal catecholamine-producing tumors has been compared in a small number of patients with paragangliomas (2–4). Given their noninvasive nature and wide availability, either imaging technique appears to represent a reasonable first step in the localization procedure, although MRI may be preferred, if available (6). MRI features suggesting paraganglioma are quite distinct and include high-signal intensity (hyperdense compared with liver) on T_2-weighted images (6, 7). In addition to more sensitive and specific detection of paraganglioma, further advantages of MRI over CT may include more detailed topographic information pertinent to surgery, no interference with surgical clips, no need for iv contrast medium, and absence of radiation exposure, the latter making MRI the method of choice for detection of pheochromocytoma during pregnancy.

If these techniques fail to localize an extraadrenal catecholamine-producing tumor, additional imaging procedures are required, including MIBG radionuclide scintigraphy, octreotide scanning, and thoracic and abdominal aortography that may permit detection of aorta-derived blood supply of extraadrenal tumors. MIBG scintigraphy, a functional rather than topographic test that allows scanning of the entire body, has proved to be superior to CT and MRI in localizing cardiac paragangliomas (3, 4, 7) and thus has recently assumed a prominent role in the localization of pheochromocytomas. The compound is taken up by pheochromocytomas, ganglioneuromas, neuroblastomas, and other neural crest tumors as well as some carcinoids. Given its noninvasive nature, marked safety, and high specificity, MIBG scanning is now considered the gold standard for localization of small adrenal lesions, bilateral adrenal lesions, metastatic deposits in patients with malignant adrenal tumors, and extraadrenal lesions, including cardiac paraganglioma (3, 4, 7). However, the high specificity of up to 100% of MIBG scintigraphy has to be balanced against its relatively low sensitivity (78%) (1). Although MIBG scanning may be considered optional in patients with biochemically proven pheochromocytoma and a documented adrenal mass, omission of an MIBG scan can lead to nondiagnosis of extraadrenal tumors or metastatic pheochromocytoma. In our patient, despite of diagnostic clinical and biochemical criteria and suggestive CT imaging studies, failure of the adrenal mass to display high signal intensity on T_2-weighted MRI images led us to suspect an extraadrenal location and to perform MIBG radionuclide scanning. Further, octreotide scanning has become a promising diagnostic tool that may provide additional information in the localization of an extraadrenal pheochromocytoma. To date, however, the diagnostic accuracy and specificity of octreotide scanning in patients with pheochromocytoma have not been studied extensively (8). Further studies in larger numbers of patients will be required to assess the diagnostic value of octreotide scanning, and to compare it with MIBG scanning.

The diagnostic value of TEE in localizing a paraganglioma has been disputed (3, 4). However, as demonstrated in our patient, TEE may provide significant additional information and details on topographic relationships that may assist the cardiothoracic surgeon in planning and conducting the surgical procedure. In addition, preoperative coronary angiography may provide the surgeon with important information about vascular supply of the tumor, thus preventing severe unexpected intraoperative hemorrhage during removal of well-vascularized tumors (2, 4). The diagnostic usefulness and definitive specificity of octreotide scanning both remain unclear because the number of patients studied was too small (8). Further studies, however, may be required to determine diagnostic accuracy of this promising diagnostic tool and to compare it with MIBG scanning.

Hypercalcemia, as demonstrated in our patient, is an uncommon but well recognized complication of pheochromocytoma. Etiologies of hypercalcemia may include coexisting primary hyperparathyroidism occurring as part of the MEN 2A syndrome, catecholamine-induced release of PTH from parathyroid glands, ectopic production of PTH by the pheochromocytoma, catecholamine-mediated osteoclastic bone resorption, and the humoral hypercalcemia of malignancy syndromes mediated by PTH-related peptide (9). In our patient, MEN 2A was ruled out by demonstration of normal pentagastrin-stimulated calcitonin levels, and by the absence of mutations in exons 10 and 11 of the RET protooncogene (10). Normalization of PTH levels and decline of serum calcium levels following successful removal of the paraganglioma suggest, that, in our patient, preoperative hypercalcemia was most likely due to either catecholamine-induced PTH release or ectopic PTH-production from the paraganglioma, with or without catecholamine-mediated osteoclastic bone resorption. In addition, hyperthyroidism, which was initially present in our patient, may also have contributed to hypercalcemia and may have delayed diagnosis. Pheochromocytoma may closely mimic thyrotoxicosis in that tachycardia and hypermetabolism are common to both. Additional similarities may include nervous irritability,

tremulousness, eye lid retraction, and excessive sweating. Thus, given this patient's clinical presentation with palpitations and sweating in the presence of hypertension, hyperthyroidism was included in the differential diagnosis. Differentiating these two entities may be particularly important because administration of a β-adrenoreceptor blocking agent to a patient with presumed hyperthyroidism may precipitate hypertensive crisis in case of a pheochromocytoma. This task may be further complicated by the fact that, in some patients with pheochromocytoma, norepinephrine-induced release of thyroid hormone may cause transient thyrotoxicosis (11). In this patient, however, hyperthyroxinemia was most likely due to ingestion of excessive amounts of levothyroxine, as thyroid function studies normalized preoperatively after thyroid hormone ingestion had been discontinued. Further, the presence of hypokalemia, hypertension, and an adrenal mass in this patient led us to consider primary hyperaldosteronism as a differential diagnosis. However, hypernatremia and metabolic alkalosis, two other features of primary hyperaldosteronism. were absent. In addition, hypokalemia disappeared as soon as her treatment regimen was changed from furosemide to phenoxybenzamine, and postoperative serum potassium levels and blood pressure measurements were consistently within normal limits. Thus, administration of a loop diuretic agent without appropriate potassium replacement most likely accounted for this patient's hypokalemia.

For practical purposes, we propose that either MR imaging or MIBG scintigraphy should be part of the preoperative localization strategy in all patients with biochemically proven pheochromocytoma. If MRI is not available or fails to display typical hyperintense signals on T_2-weighted images, or if an extraadrenal catecholamine-producing tumor is suspected for other reasons, MIBG scintigraphy may be instrumental in differentiating a nonfunctioning adrenal mass from a pheochromocytoma, correctly localizing the extraadrenal tumor and avoiding the substantial risk and unpleasant scenario of performing surgery on an incidentaloma in a patient with an extraadrenal pheochromocytoma (7). Given its high specificity and diagnostic capacity, MIBG may even be advised as an important initial diagnostic tool for the detection of pheochromocytomas and extraadrenal paragangliomas. However, this recommendation may be limited by the fact that MIBG scintigraphy is expensive and not usually available even at major medical centers. In addition, approximately 10% of pheochromocytomas, most of which are located within the adrenal gland, may be missed due to low MIBG uptake or storage capacity (12). If MIBG scanning fails to localize the tumor despite biochemical evidence of pheochromocytoma, CT or MRI should be used for detection of intra- and extraadrenal tumors. Should all these techniques fail to reveal the location of a pheochromocytoma, then selective angiography, aortography, or catheterization of the inferior vena cava for detection of catecholamine gradients may be required, followed by CT or MRI reexamination of those regions (1, 5). Although frequently advised, shooting straight can do harm to some patients. The ever elusive paraganglioma continues to remind us of the opposite: the occasional need to stay away from the obvious.

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