Extra-adrenal Pheochromocytoma: Diagnosis and Management

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Extra-adrenal pheochromocytomas (EAPs) may arise in any portion of the paraganglion system, though they most commonly occur below the diaphragm, frequently in the organ of Zuckerkandl. EAPs probably represent at least 15% of adult and 30% of childhood pheochromocytomas, as opposed to the traditional teaching that 10% of all pheochromocytomas are at extra-adrenal sites. They may be malignant in up to 40% of the cases, though conflicting data add to the uncertainty of this point. Patients with EAPs may present with headache, palpitations, sweating, or hypertension. A small percent of patients may also be asymptomatic at presentation due to nonfunctional tumors. The diagnosis is confirmed by demonstrating elevated blood and urine levels of catecholamines and their metabolites. Imaging studies to evaluate for EAPs include CT, MRI, and ^{131}I-labelled metaiodobenzylguanidine scintigraphy. Preoperative pharmacologic preparation, attentive intraoperative monitoring, and aggressive surgical therapy have important roles in achieving successful outcomes. Recent reports suggest that a laparoscopic approach, along with intraoperative ultrasound, can safely remove these tumors. EAPs recur and metastasize more often than their adrenal counterparts, making lifelong follow-up essential.

Introduction

The first reported case of pheochromocytoma is attributed to Frankel in 1886. Alezais and Peyron described extra-adrenal chromaffin tumors and called them paragangliomas in 1906. In 1912, Pick recommended that intra-adrenal chromaffin tumors be called pheochromocytomas and that all extra-adrenal chromaffin tumors be termed paragangliomas. The first successful surgical resection of a pheochromocytoma was performed by Roux in 1926, and Mayo reported the first successful removal of a paraganglioma that same year [1].

Although more properly known as paragangliomas, today these tumors are frequently called extra-adrenal pheochromocytomas (EAPs). The traditional teaching of the "10% rule," which noted that 10% of all pheochromocytomas are at extra-adrenal sites, may actually be an underestimation. A review of the literature suggests that EAPs actually constitute 15% of adult and 30% of pediatric pheochromocytomas [2]. It most commonly occurs in the 2nd and 3rd decade of life with a slight male preponderance. This is in contrast to adrenal pheochromocytomas, which typically are diagnosed in the 4th and 5th decades with a slight propensity for women [2].

These tumors can arise wherever the cells of the paraganglionic system are located. Paraganglia are chromaffin tissue complexes of the neuroendocrine system distributed along the paravertebral and para-aortic axes, extending from the cervical region down to the base of the pelvis (Fig. 1). Chromaffin cells located near the celiac ganglion migrate to form the adrenal medulla around 9 to 10 weeks of gestation. The collection of paraganglia located anterolaterally to the distal abdominal aorta between the origin of the inferior mesenteric artery and the aortic bifurcation is called the organ of Zuckerkandl.

These paraganglia are accessory tissues of the autonomic nervous system and function as the dominant source of catecholamine production in the fetus until they regress after age 3 years [3]. Failure of involution of chromaffin tissue leads to the development of paragangliomas at these sites. Eighty-five percent of EAPs are located in the retroperitoneum, usually arising from the organ of Zuckerkandl.

Less common sites reported include the bladder, thorax, neck, and pelvis [3]. Additionally, EAPs tend to demonstrate multicentricity in 15% to 24% of cases [2]. The majority of paragangliomas of the head and neck are nonfunctioning tumors of the parasympathetic system that are often brought to clinical attention by symptoms of mass effect rather than excess catecholamine. Paragangliomas that arise from the jugulotympanic body are known as chemodectomas, and those arising from the carotid body are called carotid body tumors.

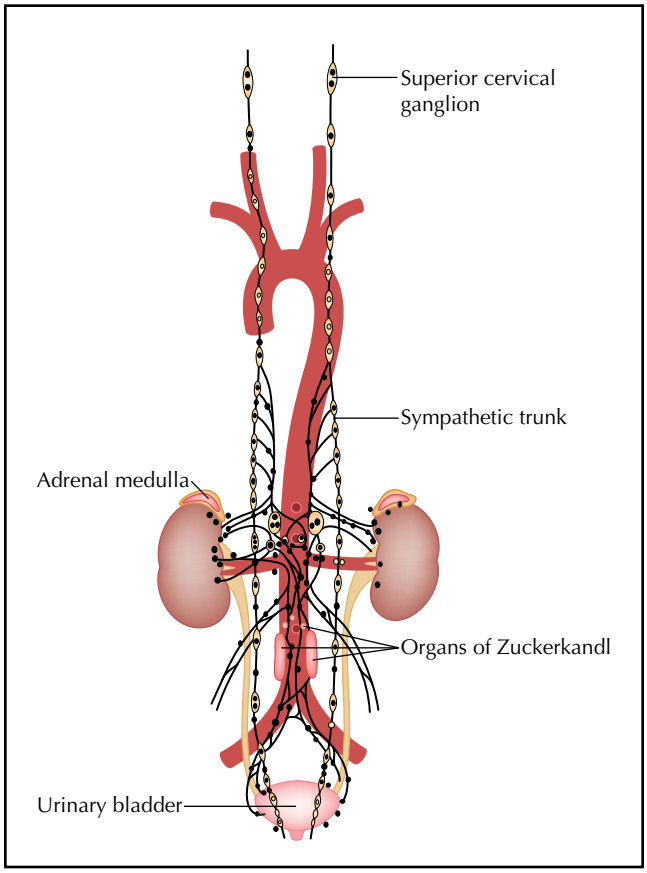

Figure 1. The paraganglion system. (*From* Ishak et al. [37]; with permission.)

A classification system for EAPs proposed by Glenner and Grimley [4] in 1974 divided the tumors into four groups based on location: branchiomeric, intravagal, aorticosympathetic, and visceroautonomic. The branchiomeric and intravagal tumors occur in the head and neck, are rarely functional, and generally stain negative for chromaffin. The aorticosympathetic group is found along the length of the aorta, between the renal arteries, around the iliac bifurcation, and includes the organ of Zuckerkandl. The visceroautonomic division occurs in association with blood vessels or visceral organs like the bladder. The latter two groups tend to be functional and usually are chromaffin positive [4].

Familial Associations

In general, pheochromocytomas located in the adrenal are familial in 10% of cases. EAPs can rarely be inherited as an isolated autosomal dominant trait or as part of the multiple endocrine neoplasia type II syndrome, as well as with neurofibromatosis and von Hippel-Lindau disease [2]. In 1977, Carney et al. [5] described a triad of EAPs, gastric leiomyosarcoma, and pulmonary chondroma. In the study by O'Riordain et al. [6], nine of 66 patients (13.6%) had first-degree relatives with pheochromocytoma. In five patients (7.6%) there was family history of EAPs. One patient had multiple endocrine neoplasia type IIb syndrome, one had von Hippel-Lindau, and two had Carney's triad [6].

Additionally, recent work elucidating mutations of the succinate dehydrogenase genes (SDHB and SDHD) has discovered another hereditary cause of paragangliomas [7]. Mutations in these genes have been seen in 3% to 11% of nonsyndromic EAPs in the head, chest, and abdomen. These tumors predominantly produce norepinephrine, occur in the head and neck, are multifocal, and may have a slightly higher rate of malignancy than other EAPs [8].

Symptoms

Although EAPs can be nonfunctional, the majority of EAPs occurring below the diaphragm are functional with the symptoms related to the excessive secretion of catecholamines, namely norepinephrine. In EAPs, the lower levels of phenyl-ethanolamine-N-methyltransferase (the enzyme responsible for the conversion of norepinephrine to epinephrine by methylation) may lead to higher production of norepinephrine [9••]. Commonly reported symptoms include hypertension (attacks and/or sustained), headaches, sweating, palpitations, anxiety, and tremors, along with a host of other symptoms and signs that have been found in patients with pheochromocytomas. The patient can also occasionally be completely asymptomatic, further obscuring the diagnosis. Functional tumors tend to be smaller when detected because of the symptoms it is capable of producing as opposed to nonfunctional tumors, which can be larger when diagnosed.

Symptoms from EAPs may also result from tumor compression of adjacent structures. Yadav et al. [10] described the 3rd reported case of an EAP presenting with unilateral ureteral obstruction. Blecha et al. [11] reported a large paraganglioma causing a small bowel obstruction. Stevenson et al. [12] reported the first known case of an EAP causing a left ileofemoral deep venous thrombosis. EAPs in the bladder can present with attacks brought on by micturition, along with various lower urinary tract symptoms. Also, EAPs located near the renal hilum have been found to cause renal artery stenosis in 75% of cases [2]. Because of the variety of clinical manifestations and nonspecific physical findings, the diagnosis of a pheochromocytoma, and especially those located outside of the adrenal, requires a particularly high index of suspicion.

Diagnosis

The diagnosis of pheochromocytomas, as well as EAPs, involves demonstrating elevated catecholamines and their metabolites in the blood and urine. Lenders et al. [8] reported on 1003 patients, 214 of which were later confirmed to have pheochromocytomas. They found that plasma-free metanephrines and urinary fractionated metanephrines offered

higher sensitivity (99% and 97%, respectively) than plasma catecholamines, urinary catecholamines, total urinary metanephrines, and urinary vanillylmandelic acid (84%, 86%, 77%, and 64%, respectively). Specificity was highest for urinary vanillylmandelic acid (95%) and urinary total metanephrines (93%) compared with plasma-free metanephrines (89%), urinary catecholamines (89%), plasma cathecholamines (81%), and urinary fractionated metanephrines (69%). Utilizing ROC curves, they deduced that at equivalent levels of sensitivity, the specificity of plasma-free metanephrines was the highest, and at equivalent levels of specificity, the sensitivity of plasma-free metanephrines was also the highest. They concluded that measurement of plasma-free metanephrines is the single best test for excluding or confirming pheochromocytomas. The high sensitivities of plasma-free metanephrines or urinary fractionated metanephrines mean that a negative test virtually excludes the presence of a functional pheochromocytoma [8].

Imaging studies are a necessity in evaluating the location, extent, and multifocality of disease, as well as for the presence of metastatic disease. CT scanning of the abdomen and pelvis is usually the first study performed. Some institutions do not use intravenous contrast for CT scans that are requested to "rule out pheochromocytoma" for fear of inciting a hypertensive crisis; however, this is not proven. For detecting pheochromocytomas in the adrenal, the sensitivity of CT and MRI ranges from 88% to 100% and from 95% to 100%, respectively, with specificity dropping to approximately 50% [13]. If a high-quality, unenhanced, and delayed contrast CT scan is performed and the tumor is localized, there is no need to proceed to MRI, but functional imaging is required to confirm that the mass is a pheochromocytomas and to rule out metastatic disease. If the CT is negative in a patient with biochemically proven disease, MRI should be performed [14••]. On T2 weighted images, pheochromocytomas have a characteristically bright appearance; however, such high signals can also be generated by hemorrhages, hematomas, adenomas, and carcinomas as well (Fig. 2). Atypical pheochromocytomas may show medium signal quality on T2 weighted images and an heterogeneous appearance, especially if they are cystic [15]. MRI is also the preferred study in detecting tumors during pregnancy, in children, or in patients with renal insufficiency or contrast allergy [14••]. Specifically regarding EAPs, Lumachi et al. [16] reported that the sensitivity for CT and MRI was 90% and 93%, respectively; the combination of MRI and MIBG was 100% sensitive and 100% specific. Others have also reported that MRI may be slightly superior to CT scan for EAPs, metastatic, or recurrent disease [16,14••,17].

The most commonly used functional study for detecting pheochromocytomas and EAPs is scintigraphy with ^{131}I-labelled metaiodobenzylguanidine (^{131}I-MIBG). MIBG is a noradrenalin analogue that is stored by most functional paragangliomas within intracellular storage granules of the presynaptic adrenergic neurons. For adrenal pheochromocytomas, ^{131}I-MIBG scintigraphy has a sensitivity ranging from 77% to 90% and a specificity of 95% to 100% [14••,17]. ^{131}I-MIBG is excellently suited as an initial localization study for EAPs. For most patients, a negative result excludes a pheochromocytomas, and focus of uptake usually confirms a pheochromocytoma [6]. It aides in preoperative surgical planning and can demonstrate multifocality or metastatic disease. They are also extremely useful after surgery and can be used to evaluate for tumor recurrence and distant metastases [3]. Scintigraphy using MIBG labeled with ^{123}I instead of ^{131}I is reported to yield superior images with less radiation exposure, with a sensitivity ranging from 83% to 100% and a high specificity (95%–100%), but the cost and shorter half-life of this isotope (13.2 hours) limits its use. Fusion imaging techniques of MIBG with CT/MRI hold tremendous diagnostic potential for the workup of the tumors [18].

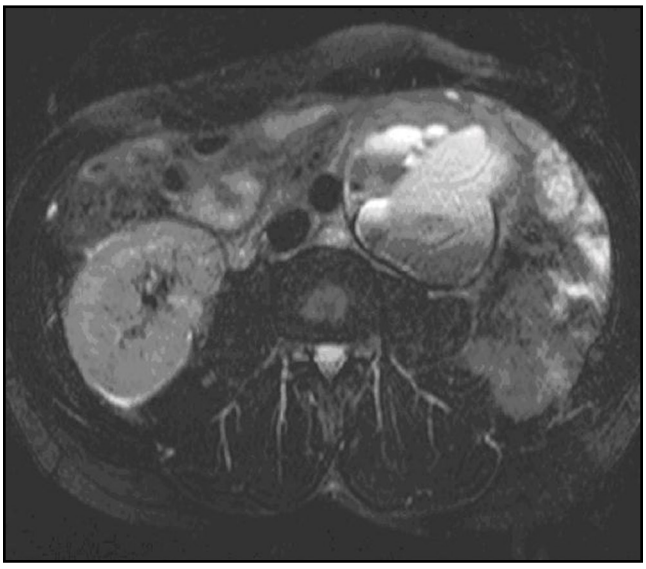

Figure 2. MRI demonstrating a left-sided extra-adrenal pheochromocytoma arising from the organ of Zuckerkandl. (*From* Lack [38]; with permission.)

Since 1990, six novel functional imaging techniques have been developed and compared with established methods. These comprise somatostatin receptor scintigraphy with ^{11}In-pentetreotide, and positron emission tomography (PET) using ^{18}F-fluorodeoxyglucose, ^{11}C-hydroxyephedrine, ^{18}F-dihydroxyphenylalanine, ^{18}F-fluorodopa, and most recently ^{18}F-fluorodopamine [14••]. ^{18}F-fluorodeoxyglucose is the only PET imaging that is widely available, but its use is recommended in cases in which other imaging tests are negative or in rapidly growing poorly differentiated tumors that have lost the ability to accumulate other specific drugs. Ilias et al. [19] reported that PET with ^{18}F-fluorodopamine had 100% sensitivity in the detection of metastatic pheochromocytoma in a recent study of 16 patients. Seven of these patients had negative ^{131}I-MIBG scans, and the

technique detected substantially more metastatic foci than ^{131}I-MIBG scanning. However, larger studies are a necessity to accurately compare PET with MIBG in terms of sensitivity and specificity.

Treatment

The traditional treatment of pheochromocytomas and EAPs consists of open exploration and resection. With advances in laparoscopic technique and highly refined preoperative imaging, laparoscopy is increasingly being used in their management. Additionally, in recent years, robotic adrenalectomy has also been reported [20]. Although induction of anesthesia, surgical manipulation, pneumoperitoneum, and hypercapnea have all been implicated as potential stimuli for catecholamine release and subsequent hypertensive crisis, laparoscopic resection has become a widely accepted approach for pheochromocytomas located in the adrenal gland [21,22]. Investigators are also performing laparoscopic resection for adrenal pheochromocytomas larger then 6 cm [23]. During recent years, the surgical treatment of EAPs has begun to parallel the paradigm shift to the minimally invasive approach. However, though there has been extensive literature on laparoscopic surgery for adrenal pheochromocytomas, there is a dearth of studies regarding the laparoscopic treatment of EAPs due to the rarity of the condition. In fact, most reports only include a group's one case report of laparoscopic resection of an EAP [24,25].

It is important to note that regardless of whether the surgical approach is open or laparoscopic, the preoperative pharmacologic blockade, as well as the tight intraoperative hemodynamic management of EAPs, is the same as for adrenal pheochromocytomas. As such, the patient should be adequately prepared for surgery with adequate hydration, α-adrenergic blockade (such as phenoxybenzamine or prazosin), and β-adrenergic blockade to control arrhythmias. The anesthesia team should be experienced with pheochromocytomas and excellent communication between the surgical and anesthesia teams is mandatory.

Janetschek et al. [22] reported their experience treating pheochromocytomas laparoscopically in 19 patients. Four cases had pheochromocytomas in extra-adrenal sites, all of which had a known hereditary disorder predisposing them to the development of the tumor. The extra-adrenal tumors ranged from 1 cm to 3.5 cm and were all in the retroperitoneum. Mean operative time for these cases was 516 minutes with a mean blood loss of 248 mL. There were no cases of intraoperative hemodynamic instability or conversion to open, and hospital stay ranged from 4 to 7 days. At their short follow-up, there were no radiographic recurrences. Additionally, the group was the first to describe removal of an EAP laparoscopically at the same time of laparoscopic adrenalectomy [22].

Hwang et al. [9••] described their results treating five patients with EAPs laparoscopically. Mean operative time was 273 minutes and mean blood loss was 119 mL. There were no intraoperative hypertensive crises and the average hospital stay was 3.8 days. One case required conversion to an open procedure due to significant tumor adhesion to the aorta and renal hilum. One patient experienced lower extremity lymphedema with a gluteal hematoma due to a positional injury. They reported no tumor recurrence at a median follow-up of 14 months. All tumors were less than 4 cm, and though size does not dictate malignant potential in these tumors, it is nonetheless interesting to note the size of the lesion that was resected laparoscopically. The authors concluded that laparoscopy can safely and effectively be used for EAPs [9••]. Furthermore, Walz et al. [26] described their experience with laparoscopic surgery of EAPs 1 cm to 4 cm. Their recommendation for the laparoscopic management of EAPs was that those cranial to the renal vessels be managed with a posterior retroperitoneal approach and those caudal to the renal vessels be approached transperitoneally.

Intraoperative ultrasound is an additional tool used by surgeons when performing laparoscopic partial nephrectomy as well as laparoscopic partial adrenalectomy; however, its role in the resection of EAPs is less clearly defined. In 1999, Kercher et al. [27] described using ultrasound to aid in the laparoscopic resection of a para-aortic EAP. Hwang et al. [9••] used intraoperative ultrasound in three of their five cases. It serves to search for lesions not seen on preoperative imaging, delineate tumor vascularity, and evaluate for local invasion. The authors believed that it greatly improved the surgical removal of the extra-adrenal lesions and felt it is an invaluable tool for laparoscopic surgeons to embrace in such cases [9••].

The chance of malignancy in patients with EAPs has been reported to range from 20% to 50%, greater than the frequently quoted 10% risk for pheochromocytomas [28]. There are no pathognomonic findings that histologically distinguish EAPs as malignant versus benign, and parameters, such as mitotic rate and nuclear atypia, have not been shown to correlate with malignant potential. Studies examining DNA ploidy, the absence of sustentacular cells, and absence of met-enkephalin staining as predictors have also demonstrated mixed findings [2]. Further, the size of the lesion has only been correlated with malignant potential in a few reports. O'Riordain et al. [6] found that tumor size greater than 5 cm was a strong predictor of persistent or recurrent disease or mortality, and Scott and Halter [29] reported that in nine cases of malignant EAPs, all tumors were greater than 6 cm; seven of these patients died from disease.

Therefore, the diagnosis of a malignant EAP is commonly made on the basis of recurrence and the development of metastasis to lymph nodes or to other organs [2]. Some authors include local invasion as a feature of malignancy as well [6]. One review suggests that 41% of EAPs arising from the organ of Zuckerkandl were malignant based on criteria of metastases and local invasion [2]. These neoplasms have

shown both lymphatic and hematogenous spread, with the most common sites of distant metastases being bone, liver, and lungs. As such, lifelong surveillance of these patients is mandatory. One group reported that the average interval from surgical resection to the development of metastasis to be 9 years [28]. Biochemical markers and blood pressure should be checked 2 weeks postoperatively and then annually. Hypertension can persist in up to 25% of patients after surgical removal; therefore, normal levels of catecholamines can assure the physician that the hypertension is due to another etiology [2]. If increased cathecholamines are detected, a search must be made for recurrent or metastatic disease at all possible sites; ^{131}I-MIBG scans can be especially useful in this setting.

Data regarding survival rates for EAPs is limited and difficult to interpret because most studies are comprised of a majority of pheochromocytomas, with only a few cases of EAPs in the study group. Some reported local recurrence rates ranging from 0% to 7%, with EAPs of the bladder demonstrating slightly better prognosis. Sclafani et al. [30] reported that in 22 patients with EAPs, 50% were classified as malignant because of the presence of metastases. Five-year and 10-year disease-free survival rates were 19% and 19% for tumors not resected and 75% and 45% for those completely resected. Median time to first metastasis was 2 months, though two patients had their first metastases 7 years after surgical resection. Once metastases occurred in their study, the 5-year survival was 36%, with median survival of 34 months. Chemotherapy (dacarbazine, doxorubicin, etoposide, and cyclophosphamide) and radiotherapy allowed some clinical responses, but a survival benefit could not be proved [30].

O'Riordian et al. [6] reported on the Mayo Clinic's experience with 66 patients with functional paragangliomas. Twenty-four patients (36%) were defined as having malignancy according to either the presence of metastases in 14 (21%) or local invasion in 10 (15%); 11 of these patients died from disease during the 8-year median follow-up (seven in the metastases group and four in the local invasion group). Fifty patients were reported to have been cured by traditional open surgical resection [6].

The recommended treatment for recurrent or metastatic pheochromocytomas is surgical removal and debulking, largely to improve symptoms and to control hypertension. Some have shown long-term survival with recurrent and metastatic cases of pheochromocytomas, which is slightly more common with EAPs as discussed [31]. In cases in which surgery cannot be performed, the management is focused largely on palliation. Medical therapy is used to stabilize a patient's blood pressure, and other options described include embolization, palliative radiotherapy, and chemotherapy (cyclophosphamide, vincristine, darcabazine). Since the 1980s, some centers have treated patients with high-dose ^{131}I-MIBG radionuclide therapy, with overall initial improvement in symptoms (75%), hormonal response (45%), and tumor size (30%) [32]. However, only 30% have a partial tumor remission and less than 5% of patients demonstrating a complete response [33–35]. Other minimally invasive techniques, such as radiofrequency ablation, have been attempted for adrenal lesions [36], perhaps the next target will be EAPs, should their location permit.

Conclusions

EAPs commonly arise in the organ of Zuckerkandl and represent at least 15% of adult and 30% of childhood pheochromocytomas. Patients with EAPs can present with symptoms similar to pheochromocytomas, asymptomatically, or due to compression of adjacent structures. The diagnosis is confirmed by demonstrating elevated blood and urine levels of catecholamines and their metabolites, and they are accurately imaged by CT, MRI, and ^{131}I-MIBG scintigraphy. PET scans hold promise for detecting metastatic disease. Recent reports suggest that a laparoscopic approach, along with intraoperative ultrasound, can safely remove these tumors. EAPs recur and metastasize more often than their adrenal counterparts, making lifelong follow-up essential.

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