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Pheochromocytoma

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Pheochromocytomas are rare tumors originating in the adrenal medulla. They may be sporadic or in the context of a hereditary syndrome. A considerable number of pheochromocytomas carry germline or somatic gene mutations, which are inherited in the autosomal dominant way. All patients should undergo genetic testing. Symptoms are due to catecholamines over production or to a mass effect. Diagnosis is confirmed by raised plasma or urine metanephrines or normetanephrines. Radiology assists in the tumor location and any local invasion or metastasis. All the patients should have preoperative preparation with α-blockers and/or other medications to control hypertension, arrhythmia, and volume expansion. Surgery is the definitive treatment. Follow up should be life-long.

Key words: pheochromocytoma, epidemiology, genetics, pathology, symptoms, radiology, treatment, surgery, medication

Introduction

Pheochromocytomas are chromaffin cell tumors derived from the neural crest. They are associated with catecholamine production and assessed by a metanephrine and normetanephrine measurements (Pacak and Wimalawansa 2015; Farrugia et al. 2017).

The World Health Organization (WHO) in its 4th edition of the "classification of endocrine tumors" (published in 2017), tumors of the adrenals are presented in two chapters labeled as "Tumours of the adrenal cortex" and "Tumours of the adrenal medulla and extra-adrenal Paraganglia" (EAP) (Lloyd et al. 2017). Tumors of the adrenal medulla are called "pheochromocytomas' (pheos) or "composite pheochromocytomas" (Lloyd et al. 2017). Composite pheochromocytoma is a tumor consisting of pheochromocytoma combined with a developmentally related neurogenic tumor such as ganglioneuroma, ganglioneuroblastoma, neuroblastoma or peripheral nerve sheath tumor (Juarez et al. 1999; Comstock et al. 2009; Lloyd et al. 2017). Tumors of the extra adrenal paraganglia comprise paraganglioma (head and neck paraganglioma and sympathetic paraganglioma), neuroblastic tumors (neuroblastoma, nodular ganglioneuroblastoma, inter-mixed ganglioneuroblastoma, and ganglioneuroma) and composite paraganglioma (Lloyd et al. 2017). The term "metastatic pheochromocytoma" is used to replace "malignant pheo" (Lloyd et al. 2017). These can occur either sporadically or in the context of the hereditary tumor syndrome (Welander et al. 2012; Burnichon et al. 2016; Crona et al. 2017).

History

The first histologically proven case of pheo has been diagnosed by Felix Fraenkel at the University of Freiburg, Germany (Bausch et al. 2017). He was a clinician who described what would be considered the

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classical signs and symptoms of pheochromocytoma in a young woman with bilateral adrenal tumors. His colleague and Professor of Pathology, Max Schottelius, performed the histological investigation and he was the first who noticed that when the tumor was fixed in Mueller's solution, which contained chromate, was a "reddish grey" in color when fresh and became brown in Mueller's solution (Bausch et al. 2017; Turchini et al. 2018).

When pathologist cuts the tumor and adds a dichromate fixative, it turns brown-black, owing to oxidation of the catecholamines stored within the granules of the chromaffin cells (Robbins and Kumar 1987; Turchini et al. 2018). To this phenomenon owes its pheo name. This "brown-black" in Greek it is called «φαιός» (pronounced pheos). "Chromo" is the Greek word for color (χρώμα) (pronounced chroma) and cytoma (κύττωμα) is the Greek word for a mass of cells. Thus, pheochromocytoma (φαιοχρωμοκύττωμα, in Greek) denotes "a mass of cells that have brown-black color. The term pheochromocytoma has been coined by Ludwig Pick in 1912, who used it to refer to tumors in the adrenals and at extra-adrenal places (Pick 1912). This characteristic was used in diagnosing pheos roughly from 1912 (Pick 1912) until the widespread use of immunohistochemistry in the 1980s (Turchini et al. 2018).

Epidemiology

Pheos are rare tumors, with an annual incidence of 2 to 9.1 per 1 million adults and may correspond up to 60% of all adrenal incidentalomas (epinephromas) (Farrugia et al. 2016) according to various studies (Kudva et al. 1999; Mantero et al. 2000; Harari and Inabnet 2011; Ramachandran and Rewari 2017; Andrade et al. 2018). The majority are benign but up to 25% may be malignant (Dahia 2017). Males and females are affected equally.

Pheos can appear in any age, however, more commonly in the 3rd to 5th decade of life (Kiernan and Solorzano 2016; Gunawardane and Grossman 2017; Fishbein et al. 2017; Rossitti et al. 2018). Hereditary disease is more likely to present in younger patients (Pamporaki et al. 2017). In children presenting with apparently sporadic pheos, up to 70% of cases as hereditary disease is discovered (Landsberg 2018).

Pheos are responsible for 0.2–0.6 of both systolic and diastolic hypertensions (Manger 2009; Farrugia et al. 2017) and rarely in isolated cases of systolic hypertension (Manger 2009).

However, about 50% of pheos are diagnosed only at autopsy because many of these tumors remain clinically silent during life (Arnaldi and Boscaro 2012; Mazza et al. 2014). The peril of missing the diagnosis of pheos is strikingly revealed by a Mayo Clinic report of 54 autopsied patients whose pheos contributed to 55% of deaths and was not suspected in 75% of cases (Sutton et al. 1981). Autopsy studies estimate the percentage of undiagnosed pheos from 0.05% to 0.09% (Minno et al. 1954; von Schlegel 1960; McNeil et al. 2000). In MEN 2A patients, cancer develops between second and third decade of the life (Morrison and Nevin 1996).

Genetics

Pheos and EAPs have the same embryonic origin, therefore they also share the same genetic characteristics. Pheos/EAPs from a genetic point of view are divided into two categories: 1) inherited and 2) sporadic cases. The 10% rule (10% are bilateral, 10% are extra adrenal, 10% are malignant, 10% are diagnosed in asymptomatic patients and 10% are hereditary) was first introduced by John Graham (Graham 1951). Recently, it has been disputed since newer studies have reported different prevalence (Neumann et al. 2002; Elder et al. 2005; Biggar and Lennard 2013; Leung et al. 2013; Gunawardane and Grossman 2017; Ramachandran and Rewari 2017). The genetic analysis of pheos offer very useful information that can be valuable in screening, diagnosis, and prognostication of hereditary pheos/EAPs (Gunawardane and Grossman 2017).

According to the Endocrine Society Clinical Practice Guidelines (ESCPG), the pheos/EAPs patients should "engaged in shared decision making for genetic testing" (Plouin et al. 1997; Lenders et al. 2014). Concerning the genetic test that should be done in pheos/ EAPs patients, guidelines can be found in the "Consensus Statement on next-generation-sequencing-based diagnostic testing of hereditary pheos/EAPs" (Toledo et al. 2017).

Genetics of pheos. Pheos may be either sporadic or a manifestation of hereditary (familial) syndromes, which are transmitted in autosomal dominant fashion (Gunawardane and Grossman 2017).

Up to 70% of pheos/EAPs carry germline or somatic mutations in one of the numerous predisposing genes (Weinstein et al. 2013; Burnichon et al. 2016; Gunawardane and Grossman 2017; Khatami et al. 2018). The incidence of mutations in Pheos/EAPs is by far higher than the 10% or less for the rest of cancer types (Dahia 2014; Favier et al. 2015; Dahia 2017). Out of this 70% of hereditary pheos/EAPs, germline mutations are responsible for approxi-

mately 40% of cases, while somatic mutations are responsible for 30% (Amar et al. 2012; Burnichon et al. 2012; Pacak and Wimalawansa 2015; Burnichon et al. 2016; Khatami et al. 2018). One third of these mutations are caused by mutations in the VHL gene (Zhikrivetskaya et al. 2017). Until now, more than 30 genes associated with inherited pheos/EAPs have been discovered (Zhikrivetskaya et al. 2017).

The germline genes are: RET, NF1, VHL, succinate dehydrogenases (SDHA, SDHB, SDHC, SDHD, and SDHAF2), TMEM127, PHD1, PHD2, HIF2A, FH, Myc-associated factor (MAX), and KIF1B (Siddiqi et al. 2012; Bayley et al. 2010; Dahia 2014). The somatic genes are: VHL, EPAS1, CSDE1, MAX, HRAS, NF1, RET, and possibly KIF1B (Siddiqi et al. 2012; Crona et al. 2013; Fishbein et al. 2017; Mercado-Asis et al. 2018; Zhikrivetskaya et al. 2017; Khatami et al. 2018).

The syndromes that are associated with pheos are: 1) Multiple Endocrine Neoplasia 2 (MEN2) which is associated with RET mutations, 2) von Hippel-Lindau syndrome (VHL), which is due to VHL gene mutations and 3) Neurofibromatosis type 1 (NF1) which is due to NF1 gene mutations (Table 1) (Burnichon et al. 2016; Farrugia et al. 2017). Germline mutations occur almost always in patients with the above-mentioned syndromes. Even sporadic cases carry high germline mutation (Gunawardane and Grossman 2017).

SDHB mutations that are frequent in patients with malignant pheos are associated with shorter survival (Amar et al. 2007).

In recent years, we had witnessed tremendous advances in molecular biology. As a result of these advances, scientists have been trying to categorize pheos/EAPs into various categories. For taxonomy purposes the molecular genetic term "cluster" is used. Some use the two clusters (Gunawardane and Grossman 2017; Dahia 2017; Mercado-Asis et al. 2018; Khatami et al. 2018) or even three clusters taxonomy (Bjorklund et al. 2016; Crona et al. 2017; Fishbein et al. 2017). Fishbein and co-authors (2017) in their study added and a fourth cluster the "cortical admixture but this is disputed by others (Flynn et al. 2015; Crona et al. 2017). In this presentation, we prefer to use the second taxonomy (three clusters), since it is based on the Cancer Genome Atlas (TCGA) (Weinstein et al. 2013; Bjorklund et al. 2016).

The tree clusters are: 1) hypoxia/pseudohypoxia, 2) Wnt signaling pathway and 3) kinase signaling group (Weingarten et al. 2010; Bjorklund et al. 2016; Crona et al. 2017).

Hypoxia/pseudohypoxia pathway. Back in 1927, Otto Warburg, a German biochemist, was the first who noticed an odd characteristic in the metabolism of cancer cells that bears his name (Warburg phenomenon). He discovered that tumor cells rely on anaerobic ATP production through glycolysis, even in the presence of normal oxygen levels in the body (Warburg et al. 1927). Usually the cells under hypoxia react to the lower O_2 in a series of reactions, which are called as the "hypoxia response". The term pseudohypoxia refers to the activation of this response in the presence of normal partial pressure of O_2 in the body. The pseudohypoxia response is a common feature of solid tumors and is characterized by increased glycolytic metabolism and promotion of angiogenesis (Majmundar et al. 2010; Huang et al. 2014). Therefore, the induction of the hypoxia pathway in tumors underlies the so-called glycolytic shift, which is a typical feature of tumors (Majmundar et al. 2010).

The hypoxia/pseudohypoxia cluster is divided in two subgroups. The first is related to germline mutations that affect Krebs cycle and especially in the succinate dehydrogenase subunits (SDHA, SDHB, SDHC, SDHD and SDHAF2), the fumarate hydratase (FH), the malate dehydrogenase 2 (MDH2), and isocitrate dehydrogenase (IDH) (Crona et al. 2017; Mercado-Asis et al. 2018). The other subgroup involves mutation VHL/EPAS1 genes (Crona et al. 2017). The second subgroup shows a bigger rate of angiogenesis and over expression of vascular endothelial-vessel growth factor (VEGF), which increases neo-angiogenesis and its receptors (Amar et al. 2012).

Because the Krebs cycle (KC) (or tricarboxylic acid cycle or the citric acid cycle) has a major implication hypoxia/pseudohypoxia response (Majmundar et al. 2010; Raimundo et al. 2011; Evenepoel et al. 2015), we shall comment on this with some details. KC is a cyclic series of enzymatically catalyzed reactions carried out by multienzyme systems (Halkertson 1988). The KC cycle is a central pathway in the metabolism of sugars, lipids and amino acids (Scheffler 2008). KC is an amphibolic pathway; it is both anabolic and catabolic. The reactions of the KC cycle occur within the inner membrane of mitochondria, in the mitochondrial matrix. Pyruvate, which is formed either from glycolysis or lactate or by transamination of alanine, can be oxidized by an enzyme complex the pyruvate dehydrogenase to acetyl CoA and CO_2. The first step of the cycle is the formation of citrate via the condensation of a four-carbon unit, oxalo-acetate, with two carbon unit, the acetyl CoA. In the sixth step, fumarate and a FADH2 are formed by succinate and FAD (flavin adenine dinucleotide) this reaction is catalyzed by the enzyme succinate dehydrogenase (SDH). In the seventh step, fumarate and H_2O react and an L-malate is formed a reaction which is catalyzed by

the enzyme fumarate hydratase (FH). In the eighth step the reaction is catalyzed by the enzyme NAD^+ linked malate dehydrogenase and an oxaloacetate is formed by an L-malate and the cycle starts again (Halkertson 1988).

Mutations on the above-mentioned enzymes lead to accumulation of succinate, fumarate and L-malate. These metabolites have oncogenic effects through inhibition of enzymes involved in cell signaling and chromatin maintenance (Raimundo et al. 2011; Castro-Vega et al. 2014; Evenepoel et al. 2015; Crona et al. 2017; Toledo and Jimenez 2018).

At increase levels succinate and fumarate deactivate KG-dependent dioxygenases. These enzymes deactivate the Hypoxia Induced Factor (HIF)-propyl hydroxylases, which degrade HIFs (Briere et al. 2005; Pollard et al. 2005; Selak et al. 2005; Lendvai et al. 2014; Evenepoel et al. 2015; Favier et al. 2015; Jochmanova and Pacak 2016; Mercado-Asis et al. 2018). Therefore, high concentration of succinate and fumarate result in the activation of hypoxia/pseudohypoxia pathway and the activation of the oncogenesis pathway (Selak et al. 2005; Lendvai et al. 2014; Evenepoel et al. 2015; Pillai et al. 2016; Mercado-Asis et al. 2018).

In addition to Pheos/EAP, SDH mutations are implicated in the pathogenesis of other tumors such as gastrointestinal stromal tumors, renal-cell carcinomas, and pituitary adenomas (Evenepoel et al. 2015).

The pseudohypoxia, the cellular response leads to epigenetic alterations in HIF target genes that affect multiple cellular processes including angiogenesis, migration, apoptosis, proliferation and tissue invasion (Semenza 2003, Favier et al. 2015, Gunawardane and Grossman 2017).

HIF is a heterodimer protein, which is composed of two units, O_2 depended subunit "α" (alpha) expressed in all cells and O_2 independent and continuously expressed "β" (beta) subunit (Jochmanova et al. 2013; Huang et al. 2014). HIF-α dimers are of three kinds, HIF-1a, HIF-2a, or HIF-3a. These make heterodimers with HIF-1b and form a heterodimeric complex, which can recognize and bind to hypoxia response elements in the genome (Huang et al. 2014). HIF-1a is ubiquitously expressed in all cells, HIF-2α is expressed preferentially in the endothelium, heart, kidney, gastrointestinal epithelium, lung, and neural crest cell derivatives (Wiesener et al. 2003; Keith et al. 2012), and HIF-3α expressed in the thymus, cerebellum, Purkinje cells, and the corneal epithelium of the eye (Makino et al. 2001).

HIF was initially identified as a regulator of erythropoietin production (Majmundar et al. 2010). The HIF when activated promotes the synthesis of erythropoietin, which results in increase in 1) red blood cell mass, 2) VEGF, which promotes neo-angiogenesis, 3) tyrosine hydroxylase, which is involved in the control of ventilation regulated by the Carotid Body, 4) regulates aerobic glycolysis, 5) prevents cancer cells from damage of hypoxic stress, 6) increases glucose uptake and lactate production.

HIF-1 blocks tricarboxylic acid cycle and oxidative phosphorylation. The HIF-1 pathway decreases mitochondrial biogenesis and itself induction of mitochondrial autophagy, as a consequence, reactive oxygen species production is decreased and benefits cancer cell survival in prolonged hypoxic condition of the cancer cells.

HIF increases triglycerides storage and fatty acids synthesis. It also suppresses carnitine palmitoyltransferase 1 and acyl-CoA synthase long-chain family member 1, which facilitate fatty acid import and oxidation, respectively resulting in blocking of fatty acids oxidation, in mitochondria (Zhu and Bunn 1999; Semenza 2010; Huang et al. 2014).

In contrary to the above, HIF is necessary for embryonic healthy development. In mammals, the embryogenesis quite often occurs under low O_2 concentrations (1–5%) and consequently HIF activity is essential for the normal development (Huang et al. 2014). Various HIFs are essential for the development of blood, placenta, heart, and vascular system (Dunwoodie 2009; Kenchegowda et al. 2017). Germline inactivation of HIF subunits results in non-viable embryos by mid-gestation with structural defects in each of these organ systems (Dunwoodie 2009).

HIFs play also a protective role in the coronary diseases, peripheral artery disease, wound healing and are critical for the transplant's survival (Semenza 2012). HIFs are also necessary for the long-term survival for people who live in high-altitude mountains (Majmundar et al. 2010).

HIFs contribute to the pathogenesis of various diseases. These are: hereditary erythrocytosis, traumatic shock, pulmonary arterial hypertension, obstructive sleep apnea, and cancer (Semenza 2012).

In cancer, HIFs activate transcription of genes that play key roles in the critical aspects of cancer biology, including stem cell maintenance (Wang et al. 2011), cell immortalization, epithelial-mesenchymal transition (Mak et al. 2010), genetic instability (Huang et al. 2007), vascularization (Liao and Johnson 2007), glucose metabolism (Luo et al. 2011), pH regulation (Swietach et al. 2007), immune evasion (Lukashev et al. 2007), invasion and metastasis (Huang et al. 2007), and radiation resistance (Huang et al. 2007).

Wnt signaling pathway. Wnt proteins are a class of proteins, which mediate communication between the cells, which are either adjacent or located in a short distance where they bind with the Frizzled/ Lrp heterodimeric receptor complexes (Wiese et al. 2018). The Wnt proteins play an important role in the development, tissue homeostasis, and organogenesis and are important for the cell survival, migration, polarization, and chemotaxis (Karvonen et al. 2018). The Wnt signaling pathway is dysregulated in various diseases such as cancer, cardiovascular diseases, bone diseases, hereditary colorectal cancer, intellectual disability syndrome, vitreoretinopathy, neuropsychiatric diseases, and other PCP-related diseases (Katoh and Katoh 2017), ("PCP-related diseases" to mean "hereditary diseases associated with the germline mutations in the PCP-related genes as well as cancers with aberrant expression or functions of PCP-related molecules" [personal communication with professor Katoh M.])

In the medical literature, signaling mutations in the Wnt cascade appear only in sporadic cases (Crona et al. 2017; Fishbein et al. 2017) with the mutations occurring exclusively in tumor cells. They are associated with mutually exclusive somatic mutations in CSDE1 or somatic gene fusions UBTF-MAML3 that cause activation of the Wnt and Hedgehog signaling (Crona et al. 2017). This kind of tumors is regarded as more aggressive (Fishbein et al. 2017).

Kinase signaling group. Kinase signaling group consists of germline or somatic mutations in RET, NF1, TMEM127, MAX, HRAS and KIF1Bβ (Crona et al. 2017; Zhikrivetskaya et al. 2017). These mutations lead to the abnormal activation of various signaling pathways associated with kinase-like proteins (Zhikrivetskaya et al. 2017). These proteins are associated with PI3 kinase pathways the "PI3K/ AKT/ mTOR and MAPK/ERK" which when activated play important roles in tumorigenesis of a wide array of tumors, including pheos/EAPs (Morrison 2012). The MAPK pathway's responsibility in the pathogenesis of pheos/EAPs has been documented by a number of studies (Hrascan et al. 2008; Crona et al. 2013).

Familial diseases of this group include; MEN2, which occurs as a result of gain-of-function mutations in RET proto oncogene (rearranged during transfection). This proto oncogene encodes a transmembrane receptor tyrosine kinase involved in the regulation of cell proliferation and apoptosis (Bryant et al. 2003).

Neurofibromatosis 1 is due to inactivation of NF1 gene, which leads to activation of RAS/MAPK and PI3/AKT signaling pathways and familial pheos/EAP related to TMEM127 or MAX (Zhikrivetskaya et al. 2017). TMEM127 mutation activates the mTOR pathway, while MAX mutation has been established to affect the downstream mTOR pathway via the MYCMAX-MXD1 network (Gunawardane and Grossman 2017).

The pheos associated with MEN2 are usually benign and bilateral. Usually an overproduction of epinephrine and consequently metanephrine is detected in the plasma and urine of these patients (Gunawardane and Grossman 2017).

The kinase signaling subtype has predominantly been observed in pheos, which also over express the enzyme "Phenylethanolamine N-methyltransferase" (PNMT) (Goldstein et al. 1972; Gunawardane and Grossman 2017). This enzyme is found primarily in the adrenal medulla and converts the norepinephrine (noradrenaline) to epinephrine (adrenaline) (Goldstein et al. 1972).

Pathology

The histologic appearance of pheos tumors is variable, they appearance varies from small to large polygonal cells having abundant basophilic to eosinophilic granular cytoplasm and pleomorphic nuclei. The cells are usually disposed in small nests or irregular trabeculae demarcated by a delicate fibrous stroma (Robbins and Kumar 1987). Pheochromocytoma is usually well circumscribed and unencapsulated. The cut surface is pink, grey, or tan and can be easily distinguished from the bright yellow of adrenal cortical tumors (Landsberg 2018).

The malignant pheos are defined only by the documented presence of metastases in non-chromaffin cells and less emphasis has been placed on the local invasion (DeLellis et al. 2004, Goffredo et al. 2013).

There is no single histologic feature of pheos that will consistently predict clinical outcome (Thompson 2002; Maitra 2010). Neither tumor size, mitotic rate, nor vascular or capsular invasion is a sufficient discriminating feature, which could serve to distinguish the benign from malignant tumors (Sternberg et al. 1999). Metastasis may appear even 5 years after the initial diagnosis (Goldstein et al. 1999). Thus, all pheos may display metastatic potential (Bozin et al. 2017).

All pheos display similar basic histopathological characteristics although some differences between familial tumors have been distinguished (Chen et al. 2010).

Kimura et al. (2014) in a study by the "Phaeochromocytoma Study Group in Japan (PHEO-J)", pheos

were analyzed using a system called grading system for adrenal pheochromocytoma and paraganglioma (GAPP). The tumors were scored based on GAPP criteria as follows: histological pattern, cellularity, comedo-type necrosis, capsular/vascular invasion, Ki67 labelling index, and catecholamine type. All tumors were scored from 0 to 10 points and were graded as one of the three types: well-differentiated (WD, 0–2 points), moderately differentiated (MD, 3–6 points) and poorly differentiated (PD, 7–10 points). They found that there was a significant negative correlation between the GAPP-score and the interval until metastasis. In this study the number of years until metastasis after the initial operation was 5.5±2.6 years (Kimura et al. 2014).

Symptoms

The key to diagnosing of pheos, is the first to think of it (Manger 2009). Similar symptoms and signs with that of pheos are manifested by numerous other clinical conditions and therefore, pheos are often referred as the "Great Mimic' (Chen et al. 2010) or the "Great Masquerader" (Reyes et al. 2018).

The symptoms are caused either by catecholamines overproduction, local pressure or metastasis. Side effects of long-standing hypertension may precipitate end organs damage in heart, kidney, eyes, central nervous system and deregulate glucose metabolism causing diabetes (Baguet et al. 2004; Pogorzelski et al. 2014).

In a series of patients with pheos discovered at autopsy, 75% died suddenly from myocardial infarction or a cerebrovascular catastrophe. Approximately one third of these sudden deaths occurred during or immediately after the unrelated minor operations (Sutton et al. 1981).

There is no single clinical finding that has significant value in diagnosis or excluding pheochromocytoma (Pourian et al. 2016). In two recent metanalyses (Pourian et al. 2016; Soltani et al. 2017), the symptoms with the greatest "pooled sensitivity" were hypertension (80.7%), headache (60.4%), palpitation (59.3%) and ephidrosis (Farrugia 2017) (diaphoresis) (52.4%). The definition of orthostatic hypotension varied between the studies and it ranged between 23–50%. Other less common signs and symptoms are fatigue, nausea, weight loss, constipation, flushing, fever, anxiety, pallor, tremulousness, weight loss, chest and abdominal pain, visual blurring, papilledema, heat intolerance, hyperglycemia, nausea and vomiting, transitory electrocardiographic changes, polyuria, and polydipsia (Adler et al. 2008; Chen et al. 2010). The classic triad of ephidrosis (diaphoresis), palpitations and headache have a reported sensitivity of 89% and specificity of 67% for pheos and in the presence of hypertension 91% and 94%, respectively (Stein and Black 1991).

Rarely can appear as "pheochromocytoma crisis", which is a live threatening condition (Tschuor et al. 2014), which presents with severe hypertension to circulatory failure and shock with subsequent involvement of multiple organ systems, including the cardiovascular, pulmonary, neurological, gastrointestinal, renal, hepatic, and metabolic systems (Guerrero et al. 2009; Scholten et al. 2013; Tschuor et al. 2014). Emergency surgery is associated with higher mortality and morbidity and it is recommended an initial stabilization of the acute crisis followed by sufficient α-blockade before surgery (Scholten et al. 2013; Crona et al. 2017; Oak et al. 2018).

Pheochromocytoma in children

The average age at presentation of pheos in children is 11–13 years with a male preponderance of 2:1 (Ludwig et al. 2007; Waguespack et al. 2010; Bausch et al. 2013; Bholah and Bunchman 2017). In hypertensive children up to 1.7% have a catecholamine secreting neoplasm (Wyszynska et al. 1992). Sustained hypertension is the most common symptoms in 60–90% of children with pheos (Ludwig et al. 2007). Other symptoms are headaches in up to 67%, nausea, sweating, palpitations, pallor, and flushing in 47–57% of children (Lenders et al. 2005; Ludwig et al. 2007). It is recommended to perform a genetic screening and lifelong follow-up in all patients (Bholah and Bunchman 2017). Surgery is the gold standard (Bholah and Bunchman 2017), preoperative preparation is the same as with adults (Waguespack et al. 2010; Bholah and Bunchman 2017; Pamporaki et al. 2017).

Pheochromocytoma in pregnancy

During pregnancy, the occurrence of pheos is even more rare and range from 1 in 15 000, to 1 in 54 000 pregnancies (Harrington et al. 1999). If it remains undiagnosed and untreated, maternal and fetal mortality amounts to 40–50% (Dean 1958; Ahlawat et al. 1999). In a study by Wing et al. (2015), they estimated the overall maternal mortality in case of pheo during pregnancy was 9.8% (95% C.I. 0.054–0.17) and the fetal 16% (95% C.I. 0.1–0.24).

Pregnancy related hypertension develops after 20 weeks thus if a pregnant woman become hypertensive

before this time, suspicion for pheos should be raised. Paroxysmal episodes of hypertension occurring throughout the entire pregnancy, severe headaches, sweating, palpitation and orthostatic hypotension are clues for pheo (Nakajima et al. 2011). Biochemical tests are the same for non-pregnant women.

Radiology for localization and staging should be done only after positive biochemical tests. MRI and ultrasound are the only imaging modalities that can be used safely during pregnancy to localize the tumor (van der Weerd et al. 2017). The preparation for operation is the same as for non-pregnant. In a study by Burgess (1979), women who were pre-treated by a-adrenergic blockade had a lower maternal and fetal mortality than those who have had no α-adrenergic blockade. The second trimester is the safest period to do surgery during pregnancy because of the risk of spontaneous abortion in the first trimester (Yumi 2008). Laparoscopic adrenalectomy is safe in pregnancy (Choi et al. 2006). It has been recommended that vaginal delivery is best avoided in pregnant women with pheos (Schenker and Granat 1982).

Differential diagnosis

(Giannini et al. 1978, Manger 2009)

The differential diagnoses of pheochromocytomas include:

1. Anxiety disorders, including Benzodiazepine withdrawal syndrome.
2. Extra adrenal paragangliomas.
3. Von Hippel-Lindau Disease.
4. Essential hypertension.
5. Hyperthyroidism.
6. Insulinoma.
7. Mercury poisoning.
8. Paroxysmal supraventricular tachycardia.
9. Renovascular hypertension.
10. Carcinoid.
11. Baroreflex failure.
12. Postural tachycardia syndrome.
13. Sleep apnea.
14. Renal failure.
15. Pseudopheochromocytoma (Severe Paroxysmal Hypertension) (Eisenhofer et al. 2018).

The cases from 10 to 15 may reveal elevated plasma and urine catecholamines and their metabolites (Manger 2009).

Biochemical tests

Catecholamines continually leak from the secretary granules and are inactivated by the enzyme catechol-O-methyltransferase (COMT) the norepinephrine is transformed into free normetanephrine and the epinephrine into free metanephrine (Schulz et al. 2004). Free normetanephrine and metanephrine circulate in the plasma in low concentrations and have short half-lives, undergoing further sulphate conjugation by sulfotransferase isoenzyme (Eisenhofer et al. 2004a; Schulz et al. 2004). In contrast to the free metabolites, sulphated metanephrines are present in 20–40-fold higher concentrations, have a longer half-life and are eliminated by urinary excretion (Comstock et al. 2009).

According to the European Society Clinical Practice Guideline (ESCPG), it is recommended that the initial biochemical testing should be plasma fractionated metanephrines or 24-hour urinary fractionated metanephrines (Lenders et al. 2014; McHenry 2017; Megias et al. 2016). If these are elevated the diagnosis is established (Lenders et al. 2002a,b; Eisenhofer et al. 2003; Lenders et al. 2014; McHenry 2017; Megias et al. 2016). Exception to this, there are small tumors (<1cm), which do not release catecholamines, and the exceptional cases of tumors which only produce dopamine (Eisenhofer et al. 2003; Pappachan et al. 2014; van Berkel et al. 2014; Pacak and Wimalawansa 2015; Megias M et al. 2016).

In the study of Lenders and Eisenhofer (2017), they have defined the upper cut-off values for plasma normetanephrines to range from 0.47 nmol/l in childhood to 1.05 nmol/l for >60 years old, metanephrines 0.45 nmol/l and for 3-methoxytyramine to be at 0.10 nmol/l. ESCPG recommends using liquid chromatography with mass spectrometric or electro-chemical detection methods rather than other laboratory methods (Lenders et al. 2014). In the study of Guerrero et al. (2009), there is a conclusion that the hormones levels correlate directly with the tumor size.

Plasma metanephrines test regarded as superior to the urine test (Lenders et al. 2002a,b; Eisenhofer et al. 2018), besides measurements of plasma metanephrines result in less false-positive test results than those of urinary metanephrines (Lenders and Eisenhofer 2017). Sensitivity of plasma metanephrines in the literature ranges from 89.5% to 100% and specificity from 79.4% to 97.6%. The urine metanephrine test shows sensitivity from 85.7% to 97.1% and specificity from 68.6% to 95.1% (Lenders et al. 2002a,b; Hickman et al. 2009; Unger et al. 2012). False-positive results are common, with a rate of 19–21% for both plasma free and urine fractionated metanephrines (Lenders et al. 2002a,b; Eisenhofer et al. 2003; Yu and Wei 2010; van Berkel et al. 2014; Lenders and

Eisenhofer 2017). Unfortunately, normal values do not exclude pheochromocytoma (Sinclair et al. 1991; Stewart et al. 1993; Shawar and Svec 1996; Eisenhofer et al. 2003).

Blood sampling should be performed at a supine position after about 15–20 minutes of i.v. catheter insertion, after overnight fasting (Eisenhofer et al. 2003). Food, coffee, caffeinated beverages, strenuous physical activity or smoking are not permitted at least for about 8–12 hours before the testing. Acetaminophen should not be taken for 5 days before the test because it can interfere with the plasma normetanephrine assay (Francis and Korobkin 1996).

The elevation of plasma metanephrines of more than 4-fold above the upper reference limit is associated with close to 100% probability of the tumor (Eisenhofer et al. 2003). Significant metanephrine elevations imply epinephrine excess, which localizes tumors to the adrenal medulla (Galati et al. 2015).

In patients with plasma metanephrine values above the upper reference limit and less than 4-fold above that limit, the clonidine suppression test combined with measurements of plasma catecholamines and normetanephrine may prove useful (Eisenhofer et al. 2003). A clonidine suppression test that does not suppress the elevated plasma normetanephrine levels to <40% after three hours of administration has a very high sensitivity and specificity (100% and 96%, respectively) for diagnosing the tumor in such a situation (Maurea et al. 1996; van Berkel et al. 2014).

Very rarely pheos is present with normal metanephrines (Proye et al. 1986; Mirallie et al. 2001; Pappachan et al. 2014; Bozin et al. 2017). Pure dopamine secreting tumors are rare and, therefore, plasma dopamine and its metabolite 3-methoxytyramine are not routinely tested in every case of suspected pheos in most laboratories (Pappachan et al. 2014). However, these tests can be useful in some cases, especially metastatic disease, as metastatic tissue lacks the mature enzymes necessary for the synthesis of catecholamines (van Berkel et al. 2014). Elevated levels of plasma 3-methoxytyramine have been suggested to be a very sensitive marker of malignant tumor when compared to the assays for plasma/urinary dopamine levels (Eisenhofer et al. 2012; van Berkel et al. 2014).

The clinical presentation of most documented dopamine secreting pheos is commonly incidental with patients being asymptomatic and normotensive (Mirallie et al. 2001). Eisenhofer et al. (2005) defines dopamine secreting pheos as tumors that produce dopamine or its metabolite 3-methoxytyramine greater than the combined concentrations of noradrenaline and adrenaline (or their metabolites).

In a study of Eisenhofer et al. (2011), they have found that increase only in methoxytyramine (indicating dopamine production) characterized 70% of patients with mutations of the genes encoding SDH. Patients with NF1 and MEN2 could be discriminated from those with VHL and SDH gene mutations in 99% of cases by the combination of normetanephrine and metanephrine. Measurements of plasma methoxytyramine discriminated patients with SDH mutations from those with VHL mutations in an additional 78% of cases.

Chromogranin A (CgA) is part of the family of granins, which are acidic glycoproteins that represent an important part of secretory dense core granules. The first chromogranin that was discovered was in adrenal medulla catecholamine secretion granules and it was named as CgA (Mirica et al. 2018).

Subsequently it was observed that serum CgA increases in patients with pheos/EAPs, as well as in other hormone secreting or non-hormone secreting neuroendocrine tumors such as gastroenteropancreatic tumors, medullary thyroid carcinoma, pituitary tumors (except of prolactinomas), neuroblastomas (Plesoianu et al. 2017). The largest amounts of CgA are within the neuroendocrine cells of the adrenal medulla and in the storage granules of the sympathetic nerves (Mirica et al. 2018). Proton pump inhibitors can raise the levels of CgA to 2–3 times (Gut et al. 2016) other conditions that can raise the CgA levels are hepatic and cardiac insufficiency, kidney dysfunction, rheumatoid arthritis, inflammatory bowel disease, and atrophic gastritis (Plesoianu et al. 2017).

Plasma levels of CgA are recommended for diagnosis and monitoring of treatment and long-term evolution in pheos (Plouin et al. 2016; Mirica et al. 2018). The ESCPG suggest assaying for CgA preoperatively in patients with normal preoperative plasma or urinary levels of metanephrine and normetanephrine (Plouin et al. 2016).

Radiology

Most pheos should be evaluated by anatomical imaging [computed tomography (CT) or magnetic resonance imaging (MRI)] followed by functional imaging (nuclear medicine modalities) (Shulkin et al. 2006). Imaging studies are important for tumor localization and delineation of its extent (Ramachandran and Rewari 2017). They are also important in

diagnosing multiple primary tumors and/or metastatic lesions in patients with various genetic disorders (Ramachandran and Rewari 2017).

In a study of Mantero et al. (2000), pheos constituted the 11% of all epinephromas (Farrugia et al. 2016) (adrenal incidentalomas).

Only clinically manifested pheos are already several centimeters in size and can be detected by ultrasound in 90% of cases (Hofer 1999). On ultrasound, pheos have a variable appearance ranging from solid (75% in one case series) to mixed cystic and solid to cystic (Bowerman et al. 1981).

CT is the radiological modality of choice for localizing pheos (Lenders et al. 2014). A CT scan can show tumors >1 cm in size with 87% to 100% sensitivity (Townsend et al. 2012). Because of their varied clinical, imaging, and pathologic appearances, accurate diagnosis of pheos can be challenging (Leung et al. 2013).

Gross features of pheos in a CT scan described in the radiology literature are cystic regions (Melicow 1977), calcifications (Melicow 1977), fibrosis (Melicow 1977), necrosis (Dunnick and Korobkin 2002), and internal hemorrhage (Dunnick and Korobkin 2002). Pheos are often well-defined masses with attenuation values similar to those of muscle tissue, measuring approximately 30–40 HU (Miyake et al. 1989). Sometimes though may have attenuation values less than 10 HU and also may display more than 60% washout of contrast agents on delayed scanning. Pheos should be included with adenomas in the differential diagnosis both for masses with low attenuation on unenhanced CT and for lesions exhibiting a high percentage of contrast washout (Blake et al. 2003).

I.V. administration of non-ionic contrast material for CT is a safe practice for patients with pheos and related tumors even without α-blocking medication (Bessell-Browne and O'Malley 2007).

The adrenals can be delineated in nearly all the patients with MRI (Moon et al. 1983; Schultz et al. 1984; Chang et al. 1987; Newhouse 1990; Lee 1998). An MRI evaluation of the adrenals should usually consist of both T1- and T2-weighted images (Lee 1998). Dynamic serial T1-weighted images obtained after intravenous administration of gadolinium diethylene-triamine penta-acetic acid (Gd-DTPA) are used to show enhancement patterns of adrenal masses (Krestin et al. 1989).

The classic imaging feature for pheos is a "lightbulb" bright lesion on T2-weighted imaging comparable to the signal intensity of CSF (Elsayes et al. 2004).

MRI should be performed in large tumors prior to surgery to assess vascular invasion (Schteingart et al. 2005). MRI is the modality of choice for children and pregnant women (Harari and Inabnet 2011).

Functional imaging (FI)

Nuclear medicine modalities can be categorized into those that are specific for the catecholamine synthesis/secretion pathway and those that are nonspecific. They reflect other aspects of tumor pathophysiology (Shulkin et al. 2006). Shulkin et al. (2006) proposed that FI be performed in all patients with extra-adrenal, metastatic, or multiple pheos, norepinephrine secreting pheos, and epinephrine-secreting pheos larger than 5 cm in diameter. They also advise FI in post-surgery patients when biochemical testing in inconclusive and in particular when anatomical imaging is negative (Shulkin et al. 2006). Various substances have been used for functional imaging of pheos.

Functional imaging examinations are performed using 131I- and 123I-metaiodobenzylguanidine (MIBG), 111In-pentetreotide, and several PET ligands including 18F-fluorodopamine, 18F-dihydroxy-phenylalanine (DOPA), and 18F-FDG (FDG) 131I- and 123I-Metaiodobenzylguanidine (Ilias and Pacak 2004; Shulkin et al. 2006; Havekes et al. 2008; Leung et al. 2013).

The ESCPG (Plouin et al. 2016) suggests screening for metastatic tumors by [18F]-fluorodeoxyglucose positron emission tomography/computed tomography (FDG PET/CT), if possible, preoperatively in cases of 3-methoxytyramine (3MT) in plasma or urine; and in patients carrying germline mutations of the SDHB gene.

It is recommended to start with the following specific FI modalities: MIBG scintigraphy or PET with 18-F-DA, 18-F-DOPA, or [11C]meta-hydroxyephedrine and if in case that these turn out to be negative, nonspecific modalities (somatostatin receptor scintigraphy or FDG-PET) should follow (Shulkin et al. 2006).

In the metastatic cases, 18F (DOPA) and 18fluorodopamine-PET (FDA) were the FI tests most successful at identifying disease missed by CT/MRI, providing additional benefit in 6/60 (10%) and 5/78 (6.4%) cases, respectively (Jimenez and Waguespack 2015).

Imaging for VHL, NF1 or RET mutations is preferred the use in 18F-FDA or 18F-FDOPA. In the case of VHL, up to 80% of pheos tend to be bilateral and 18F-FDA is superior to MIBG due to the low

expression of noradrenalin membrane transporter in these case (Pacak et al. 2001a; Ilias and Pacak 2004; Havekes et al. 2010; Renard et al. 2011; Megias et al. 2016).

Treatment

The evaluation and management of patient with pheos should be multidisciplinary with appropriate expertise to ensure favorable outcomes (Lenders et al. 2014). Adequate preoperative evaluation is crucial before surgery for patients with pheos (Pappachan et al. 2014; Gregory et al. 2017; Naranjo et al. 2017). Preoperative evaluation should include a thorough patient's and family history, complete blood count, metabolic profile, plasma metanephrines, ECG and cardiac ultrasound (to check for cardiac compromise).

Pheo has pathophysiological characteristics of low blood volume, hypertension, and high blood concentrations of catecholamine which can lead to catecholamine cardiomyopathy (Harari and Inabnet 2011; Renard et al. 2011; Pappachan et al. 2014; Sanford et al. 2015; Gregory et al. 2017; Ramachandran and Rewari 2017; Weiner et al. 2017). Cardiomyopathy due to pheo is reversible (Pappachan et al. 2014). Therefore, hypertension control and improvement of blood vessel capacity are extremely important for improving surgical safety before surgery (Li and Yang 2014; Pappachan et al. 2014; Naranjo et al. 2017). In order to correct catecholamine-induced volume contraction and to prevent severe hypotension after tumor removal, it is advisable to administer preoperative high sodium diet and increase oral fluids intake and/or I.V. fluids (Lenders et al. 2014; Bednarczuk et al. 2016). Surgery is the only definitive treatment of pheos.

Preparation for surgery

Intra-operative risks must be kept to a minimum by appropriate pre-operative medical treatment to block the effects of catecholamines for at least 10–14 days before surgery (Pacak 2007; Pacak et al. 2007; Lenders et al. 2014; Mazza et al. 2014; Bednarczuk et al. 2016; Ramachandran and Rewari 2017), some authors recommend up to 21 days (Pappachan et al. 2014). Adequate pre-operative α-blockade has been proven to reduce the number of perioperative complications to less than 3% (Goldstein et al. 1999).

The three perioperative phases most associated with hypertensive episodes are endotracheal intubation, the creation of pneumoperitoneum (in cases of laparoscopic adrenalectomy), and manipulation of the adrenal gland (Kercher et al. 2005; Bruynzeel et al. 2010; Weingarten et al. 2010; Brunaud et al. 2014). Significant hypotensive episodes also can occur and are associated with a sudden decrease in catecholamine levels after removal of the tumor (Kinney et al. 2005; Ramachandran and Rewari 2017).

Alpha-blockade has been the standard management preoperatively to prevent intraoperative hemodynamic instability during resection of a pheos (Lenders et al. 2014; Pappachan et al. 2014; Malec et al. 2017).

Oral phentolamine is not used any more for preoperative preparation (Lentschener et al. 2011), it is reserved only for emergencies in the IV form (Lentschener et al. 2011; Renard et al. 2011; Pappachan et al. 2014; PDQ Board 2018). Alpha-adrenoreceptor blockers that are used most often for preoperative preparation are phenoxybenzamine (phen) and selective competitive α1-adrenoceptor blocking agents, such as terazosin and doxazosin (dox) that have shorter half-lives and lower the risk for postoperative hypotension (Chen et al. 2010). In the study of Malec et al. (2017), no clinical differences between phen and dox have been shown. Side effects of a1-adrenergic blockers include postural hypotension, syncope, and nasal congestion and they necessitate careful titration (Lentschener et al. 2011).

Alternatives to phen for preoperative blockade of catecholamine induced vasoconstriction include Calcium Channel Blockers (CC-Bs). CC-Bs also have been shown to lessen the risk of intraoperative hemodynamic instability (Brunaud et al. 2014) but it is controversial if one regimen is superior (Brunaud et al. 2014).

A β-adrenoceptor blocker may be used for preoperative control of tachyarrhythmias or angina. However, loss of β-adrenoceptor-mediated vasodilatation in a patient with unopposed catecholamine induced vasoconstriction can result in dangerous increases in blood pressure. Therefore, β-adrenoceptor blockers should never be employed without first blocking α-adrenoceptor mediated vasoconstriction (Lentschener et al. 2011; Bednarczuk et al. 2016). β-blockers that are in use for preoperative preparation are propranolol, atenolol, and metoprolol and lavetalol (Lentschener et al. 2011). Lavetalol is a β-blocker with some α-blocker properties and has the side effect of producing paradoxical hypertension (Poopalalingam and Chin 2001; Lentschener et al. 2011).

Volume contraction associated with chronic vasoconstriction can be seen in patients with pheos. Therefore, pre-operative volume expansion achieved by saline infusion or increased water intake is recom-

mended to reduce post-operative hypotension (Hack 2000; Chen et al. 2010).

Hypoglycemia after resection of pheos is a rare and poorly understood complication thought to be secondary to rebound hyper-insulinemia and increased peripheral glucose uptake. In the study of Chen et al. (2014), they have examined the incidence of this complication and aimed to identify predisposing risk factors. They concluded that their data demonstrate that hypoglycemia is a rare complication after resection of pheos and may be more common in patients with epinephrine-predominant neoplasms and longer operative times (Chen et al. 2014).

Metyrosine, inhibits tyrosine hydroxylase, which catalyzes tyrosine to dihydroxyphenylalanine (DOPA), the first and the rate limiting step of the catecholamine synthesis pathway, thereby resulting in reduction of catecholamines and their metabolites (Steinsapir et al. 1997; Naruse et al. 2018). In a study from Japan by Naruse et al. (2018), they have concluded that it was well tolerated and relieved symptoms by reducing excess catecholamine in pheos patients under both preoperative and chronic treatment. Death, failure of treatment and variation in intraoperative blood pressure in metyrosine patients were reported (Thanapaalasingham et al. 2015; Naruse et al. 2018).

All the above that have been constituted the principles of preoperative preparation for pheos surgery were disputed in some recent studies. Preoperative fluid administration was disputed by some authors (Lentschener et al. 2011). Pre- and intraoperative hypovolemia have never been demonstrated in patients scheduled for pheos removal (Desmonts and Marty 1984; Lentschener et al. 2011). Newer studies measuring the Δ-down wave during operation suggested that reduced preload associated with hypovolemia is not a major mechanism of hypotension following pheos removal (Mallat et al. 2003). In the same study they concluded that predominant mechanism of severe hypotension following tumor resection is likely to be a decrease in arterial tone and that severe hypotension may occur even to patients with normal pressure (Mallat et al. 2003).

Concerning the preoperative preparation with hypotensive medication, the majority of studies do not compare groups with medication and placebo (Lentschener et al. 2011). Regarding the preoperative blood pressure (BP) status Lentschener et al. (2009) found no relation of preoperative high BP with intra- or postoperative hemodynamic instability, the same was found in another study (Groeben et al. 2017). In the contrary to this, Plouin et al. (2001) found an association of preoperative high BP with intra- and postoperative complications. Until a new consensus, based on several double-blind studies, recommends differently, we must stick to the ESCPG guidelines and prescribe preoperative hypotensive medications. We believe that with the current knowledge, it is a malpractice not to administer hypotensive medication preoperatively.

Prophylaxis from vein thrombosis is mandatory (Gagner et al. 1997).

Surgery

Although the first successful surgical resection of a clinically recognized pheo removal is credited to Dr. Charles H. Mayo from USA in 1927 (Mayo 1927), the first operation was actually performed on 25 February, 1926 by César Roux (1857–1934) in Lausanne, Switzerland (Welbourn 1987). Dr. Mayo had his work published one year earlier than Roux, whose case was included in the thesis of Roland von der Muhll, a pathologist working in Lausanne, published in 1928 (Mayo 1927; Papadakis et al. 2016).

Surgical treatment in the past required an open laparotomy with early control of the main adrenal vein and bilateral as well as extra adrenal exploration. This practice has changed by the exquisite sensitivity of current imaging techniques and use of laparoscopic adrenalectomy (LA) (Udelsman 2001). In our days, adrenalectomy for pheos is reported with a mortality close to zero in recent studies (Lentschener et al. 2011).

Gagner et al. (1992) have reported the first laparoscopic adrenalectomy. LA has become the operation of choice and has replaced the open technique (Toniato et al. 2007). LA is of two kinds, either using transperitoneal or retroperitoneal approaches (Gagner et al. 1997; Ludwig et al. 2007). Comparing open adrenalectomy and LA, there is no statistically significant difference in age, sex, unilateral versus bilateral, blood transfusion, intraoperative hypotension and postoperative hypertension (Goldstein et al. 1999). LA is safe, effective, has shorter hospital stay, earlier resumption of oral intake, better cosmetic results, less analgesia and rapid recovery (Tanaka et al. 2000; Toniato et al. 2007; Lang et al. 2008). LA was associated, with longer operating room time and higher cost (Prinz 1995; Brunt et al. 1996; Saffarini 2007).

In experience hands LA facilitates the identification of the main adrenal vein on both sides, minimizes manipulation of the pheos and decreases circulating levels of catecholamines (Goldstein et al.

1999; Toniato et al. 2001; Cheah et al. 2002). In the beginning of LA era, arbitrarily the size limit was restricted at 6 cm due to fear for cancer (Cho et al. 2013; Eisenhofer et al. 2004b; Thomson et al. 2004). This was rejected in subsequent studies (Cheah et al. 2002; Toniato et al. 2007; Brito et al. 2015; Rao et al. 2016).

In bilateral diseases, Rossitti et al. (2018) have recommend that in case that there is a known mutation before surgery that adrenal-sparing surgery (e.g. to leave the adrenal cortex in situ) should be the standard approach for patients who have already been diagnosed with MEN2 or VHL when operating on the first side, whereas complete removal of the affected adrenal gland(s) is generally recommended for patients with SDHB or MAX germline mutations. Despite the fact that adrenal medulla is left in situ, postoperative ipsilateral recurrence rates of 3–7% have been reported after a median interval 8.5–9.5 years (Grubbs et al. 2013; Castinetti 2015; Rossitti et al. 2018).

Medication

In the cases of inoperative and malignant pheos, the chronic medical treatment is the same as the preoperative treatment (Naruse et al. 2018). The management of metastatic pheos remains palliative (Baudin 2013). Life expectancy expressed in 5-years survival ranges in most from 40–77% (Chrisoulidou et al. 2007, Nomura et al. 2009). Tumor progression is the most frequent cause of death from metastatic pheos. This clearly indicates that controlling tumor growth should be the primary goal of metastatic pheos management (Amar et al. 2007; Havekes et al. 2008). 30% of deaths are due to high levels of catecholamines which manifest as hypertension and constipation (Baudin 2013).

Surgery for malignant pheos is rarely curative, but resection of a primary mass or metastases can reduce exposure of the cardiovascular system and organs to toxic levels of circulating catecholamines or relieve organs that the metastasis place patient's life in immediate danger, e.g. heart (Mishra et al. 2000; Nonaka et al. 2000).

In cases that surgical resection is not feasible, alternative include external beam radiation, cryoablation, radiofrequency ablation, transcatheter arterial embolization, chemotherapy, and radiopharmaceutical therapy (Kawashima et al. 1999; Pacak et al. 2001b). In a study, high dose 131I-MIBG may lead to long-term survival in patients with malignant pheos (Crona et al. 2013).

Molecular targeted therapies that included everolimus, imatinib, sunitinib, had been used with various results (Baudin 2013).

Follow-up

It is recommended a life-long follow up (Jaroszewski et al. 2003; Lenders et al. 2014; Press et al. 2014; Plouin et al. 2016). Laboratory values of plasma and urinary catecholamines that should be obtained within the first month after surgery, again at 6 months, and 1 year, and imaging at 1 year. Laboratory values should be obtained annually, thereafter if everything appears to be normal (Jaroszewski et al. 2003; Plouin et al. 1997; Lenders et al. 2014; Press et al. 2014; Plouin et al. 2016). ESCPG require the addition of 3MT test 2–6 weeks after recovery from surgery in patients who had elevated 3MT levels preoperatively (Plouin et al. 2016). They also suggest assaying plasma chromogranin A levels every year in patients operated on for metanephrines negative, 3MT negative and chromogranin A-positive pheos to screen for local or metastatic recurrences or new tumor. Imaging tests should be done every 1–2 years in patients with biochemically inactive pheos to screen for local or metastatic recurrences or new tumors (Plouin et al. 2016).

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