Acute Adrenal Conditions: Pheochromocytoma Emergencies

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Pheochromocytoma and paragangliomas (PPGL) are rare chromaffin cell tumors characterized by the production of catecholamines and their metabolites and that can be fatal if left undiagnosed. The diagnosis and management of these neoplasms may result in very challenging due to the organ-specific effects of high production of catecholamines and their related consequences [1, 2].

Unfortunately, since these neuroendocrine tumors are often not recognized or misdiagnosed and consequently not well treated, they may present in several possible situations that could evolve suddenly or slowly to true emergency conditions [1].

63.1 Introduction

Learning Goals

- Although rarely, pheochromocytomas and paragangliomas may request an emergency treatment.
- The effect of catecholamines may result in several acute presentation, mostly related the cardiovascular system.
- A prompt diagnosis is crucial to perform the correct treatment.

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63.1.1 Epidemiology

Pheochromocytomas and paragangliomas are relatively rare catecholamine-producing tumors with an estimated annual incidence of 2–8 per million population. They occur mostly between the third and the fifth decades of life, although 20% of cases occur in pediatric age. Both genders are affected equally. Moreover, the prevalence among hypertensive patients ranges between 0.1% and 0.6% in adults and between 2% and 4.5% in the pediatric population [3].

PPGL are diagnosed incidentally during imaging scans in 10–49% of cases and 4–8% of adrenal incidentalomas are pheochromocytomas.

Overall, among these catecholamine-producing tumors, 80–85% are pheochromocytomas and 15–20% are paragangliomas [3].

63.1.2 Etiology

Pheochromocytomas and paragangliomas occur as sporadic tumors or in a familial context. It is reported that around 24–27% of cases carry a germline mutation [4, 5]. Nowadays, genetic screening plays a key role in diagnosis [6].

The main syndromes associated with pheochromocytoma are multiple endocrine neoplasia type IIA (MEN-IIA), von Hippel-Lindau (VHL) disease, or neurofibromatosis type I (NF-1). Multiple endocrine neoplasia type IIA consists in

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the familial association of medullary thyroid cancer, pheochromocytoma, and parathyroid hyperplasia. Patients affected by von Hippel-Lindau disease are characterized by the association of the following conditions with early onset: bilateral kidney tumors and cysts, pheochromocytomas, pancreatic tumors, cerebellar and spinal hemangioblastomas and retinal angiomas [7]. Hallmark of neurofibromatosis 1 includes cafè-au-lait spots, neoplasms of the peripheral and central nervous systems and cutaneous neurofibromas. Moreover, pheochromocytomas are reported to be associated with NF-1: their incidence is approximately 0.1–5.7% and it increases to 20–50% in patients with hypertensive status [8].

Overall, hereditary pheochromocytomas are typically intra-abdominal and bilateral and present an earlier onset compared to those with sporadic disease [7].

63.1.3 Classification

According to the updated 2017 World Health Organization (WHO) Classification of Tumors of Endocrine Organs, the term pheochromocytoma is referred to intra-adrenal tumor, whereas similar tumors arising outside the adrenal gland are defined as extra-adrenal paragangliomas and further named on the basis of their anatomic origin. Moreover, the well-known 10% rule (10% familial, 10% malignant, and 10% extra-adrenal) for sympathetic paragangliomas is no longer considered applicable since the rate of heritable lesions is reported to be up to 30% [9].

Notably, it is worth to be taken into account that around 10% of pheochromocytomas and 30–40% of paragangliomas are malignant [10]. Although scoring systems for histological evaluation of PPGL are reported, it is not possible to differentiate benign from malignant lesions by histopathology. The evidence of malignancy in these tumors can be defined for the presence of invasion of adjacent tissues or metastasis at presentation or during the follow-up [3, 10].

63.1.4 Pathophysiology

PPGL are tumors that release in the bloodstream an excess of catecholamines and therefore enhances the sympathetic nervous system leading to symptoms such as hypertension and palpitations, headaches, and sweating. Catecholamine production takes place in both the adrenal gland, as well as sympathetic paraganglia [11].

The secretory pattern of PPGL varies considerably on the basis of the type of tumors and depends on the pathway of the intracellular enzymes dedicated to product catecholamines. It is suggested that pheochromocytomas typically produce epinephrine, whereas paragangliomas have predominant or exclusive secretion of norepinephrine [12, 13]. Moreover, certain PPGL can secrete dopamine, sometimes in isolation, due to the lack of dopamine-β-hydroxylase [14].

Moreover, it is reported that among hereditary PPGL, the pattern of catecholamine production can depend on the underlying mutation. In particular, patients affected by von Hippel–Lindau syndrome are characterized by typical norepinephrine production, whereas patients affected by MEN type 2 are characterized by a production of a mixture of epinephrine and norepinephrine. Noradrenergic tumors and adrenergic tumors have distinct patterns of gene expression that are retained even when there is no clear hereditary basis [12].

On a biochemical point of view, norepinephrine typically acts on alpha-1, alpha-2, and beta-1 receptors, leading to the clinical presentation characterized by sustained hypertension. On the other hand, epinephrine mainly stimulates beta-1 and beta-2 receptors and patients with predominantly epinephrine-secreting tumors exhibited paroxysmal hypertension attributed to episodic catecholamine release and beta-2 receptor-mediated vasodilatation in skeletal muscles. Finally, the hemodynamic effects of dopamine are mainly related to the dose of the hormone in the bloodstream. Indeed, when the serum levels of dopamine are within the normal ranges, this catecholamine acts mainly on dopamine receptors, resulting in renal artery dilatation and negative cardiac inotropic action [15, 16]. On

the contrast, as the dopamine serum concentration rises, dopamine can stimulate alpha- and beta-adrenergic receptors, resulting in variable degrees of hypertension and tachycardia. As a result, patients with dopamine-secreting tumors may exhibit labile blood pressure, varying from normotension to postural hypotension or hypertension [17].

63.2 Diagnosis

Although PPGL are diagnosed and treated rarely in the Emergency Unit, they represent an important entity to be considered in the setting of differential diagnosis of several clinical presentations. PPGL may present with a wide spectrum of clinical presentations, ranging from a multisystemic or hypertensive crisis to more subtle symptoms masquerading as anxiety attacks [7]. It is crucial to not overlook the possibility of PPGL in case of an emergency situation where the conventional therapy fails to achieve control. Physicians must keep in mind this rare entity and try to obtain a prompt diagnosis in order to undertake an adequate therapy.

Diagnosis of PPGL is obtained via biochemical confirmation of catecholamines excess, followed by anatomical localization of the tumor(s).

63.2.1 Clinical Presentation

Excess release and high levels of circulating catecholamines are responsible for the typical symptoms. Characteristically, patients present with hypertension (sustained or, most often, paroxysmal), usually associated with the classic triad of headache, palpitations, and sweating [7]. Furthermore, patients with elevated levels of circulating catecholamines may suffer of an anxiety status and a sense of impending doom.

This wide spectrum of signs and symptoms has led to the label pheochromocytoma as "*the great masquerader*" since the clinical presentation is often nonspecific and raises up the suspicious of more common conditions, such as hypertension, arrhythmias, and anxiety and thus leading to acute or chronic complications without obtaining a correct diagnosis [1]. Moreover, it is reported that patients with mild hypercatecholaminemia can be relatively asymptomatic or mildly symptomatic and the disease may remain undiagnosed [1].

Nevertheless, severe hypercatecholaminemia is markedly symptomatic and may require emergency interventions due to the high risk of morbidity and mortality. In this situation, the clinical suspicion is an absolute cornerstone of the management and an eventual delay in diagnosis is adversely proportional to the overall outcome. Hereby we reported the acute conditions associated with PPGL which require an emergency management. Main clinical presentations are summarized in Table 63.1.

63.2.1.1 Multisystemic Failure

Even though multisystem failure (MSF) is a rare presentation of pheochromocytoma, it represents the most deadly complication due to its high morbidity and mortality and its rapid and unpredictable evolution and requires a prompt detection. This feared condition is defined as multi-organs failure usually associated with a temperature greater than 40 °C, hypertension or hypotension and encephalopathy [18]. Notably, multisystemic failure is not synonymous with malignant hypertension: indeed, several cases are reported in which this condition is associated with a normotensive or hypotensive status [19, 20]. Moreover, although MSF is usually preceded by hypertensive crisis, it may occur with mild and unspecific symptoms, especially in fragile patients. Besides,

Table 63.1 Main clinical presentations of PPGL

Emergency presentations	Elective presentations
Multisystemic crisis	Asymptomatic
Hypertensive crisis	Paroxysmal hypertension
Severe hypotension/ cardiogenic shock	Sustained hypertension
Ventricular tachyarrhythmias/ fibrillation	Headaches, palpitation, sweating
Pulmonary edema	Supraventricular arrhythmias
Acute coronary syndrome	Anxiety status, sense of impending doom

MSF may be associated even with less common signs and symptoms, such as abdominal pain, nausea, back pain, anemia, dyspnea, and renal failure [20].

Pheochromocytoma multisystemic crisis can occur spontaneously or may arise from the manipulation of the tumor, from an abdominal trauma or surgery, or the use of some medications [21–23].

Overall, pheochromocytoma multisystemic crisis is associated with a high mortality rate and clinical outcomes mostly depend on delays in diagnosis and the time of initiation of an appropriate therapy [24].

63.2.1.2 Hypertensive Crisis

Pheochromocytoma hypertensive crisis is a life-threatening condition secondary to a massive catecholamines secretion into the bloodstream and may result in severe complications, such as cardiovascular collapse, pulmonary edema, and sometimes acute respiratory failure with deadly outcomes [25]. The crisis is usually sprung from severe stress or pain, trauma, postural changes, local manipulation, all conditions which increase the intra-abdominal pressure or administration of some medications. Anyway, the spontaneous hypertensive crisis has been reported without any exogenous stress [26, 27]. As previously reported, this condition is most often related to norepinephrine-secreting tumors, which leads to alpha 1-adrenoceptors mediated peripheral vasoconstriction [26].

63.2.1.3 Hypotension and Cardiogenic Shock

It is of paramount importance to keep in mind that, occasionally, pheochromocytoma may present with severe hypotension: this clinical presentation occurred in the case of tumors that secrete mainly epinephrine. Indeed, epinephrine acts mainly on beta2-adrenoceptors, which leads to peripheral vasodilatation [25]. Besides, hypotension may also be secondary to the sudden cessation of catecholamines secretion after pheochromocytoma removal in a patient with very low circulatory volume secondary to vasoconstriction and desensitized beta-adrenoceptors [28]. It is reported in the literature that around 20% of patients affected by pheochromocytoma may have hypotension; further, up to 2% of patients may present with cardiogenic shock [29].

Cardiogenic shock is typically caused by pump failure due to severe left ventricular dysfunction. However, it should be remembered that severe hypotension may be due to severe left ventricular outlet tract obstruction as a complication of mid-apical Tako-Tsubo triggered by PPGL: it is crucial to not overlook this complication since its treatment differs completely from the one of cardiogenic shock caused by cardiac pump failure [25].

63.2.1.4 Arrhythmias

It is well known that PPGL have been reported associated with several forms of tachyarrhythmias, usually perceived by the patients as palpitations [30]. Lenders et al. reported that around 50–70% of patients affected by pheochromocytoma experienced palpitations [31].

Arrhythmias are related to the action of catecholamines on beta-adrenergic receptors. Although usually supraventricular, including atrial fibrillation and flutter, pheochromocytoma may be rarely associated with serious and potentially fatal ventricular arrhythmias, such as ventricular tachyarrhythmias, ventricular fibrillation, and torsade de pointes [25].

63.2.1.5 Acute Coronary Syndrome

Patients affected by PPGL may also be presented with symptoms, laboratory and ECG finding suggestive of the acute coronary syndrome. This worrisome complication is due to the action of catecholamines which leads to vasoconstriction of the coronary arteries along with an increasing oxygen request from the myocardial tissue sustained by the stimulation of the heart rate and contractility [2].

Distinguishing patients with acute coronary syndrome sustained by pheochromocytoma or heart disease may be very challenging. Retrosternal pain radiating to both upper limbs, palpitations, and anxiousness are commonly shared, as well as ECG findings [32].

On the other hand, severe hypertension accompanied by headache and profuse sweating, and history of paroxysmal attack may be suggestive of pheochromocytoma. Furthermore, if coronary arteries appear normal at angiography a pheochromocytoma should be suspected [2].

63.2.1.6 Myocarditis and Cardiomyopathy

Pheochromocytoma may present even as myocarditis or cardiomyopathy. These conditions may be related to direct myocardial toxicity of prolonged high levels of catecholamines, as well as prolonged hypertension or a coronary event. Three types of cardiomyopathies are reported: dilated, hypertrophic, and Tako-Tsubo like [32].

Clinically, patients may present a congestive heart failure, hypotension, pulmonary edema, or cardiogenic shock associated with diffuse left ventricular dysfunction [33, 34].

The myocardial changes documented in the case of cardiomyopathy sustained by pheochromocytoma usually improve after the administration of appropriate pharmacologic medications and resection of the tumor [32].

63.2.1.7 Pulmonary Edema

Rarely pheochromocytoma may manifest as pulmonary edema (PE). In this cohort of patient, pulmonary edema has usually a cardiogenic origin; nonetheless, noncardiogenic PE is reported and is believed that this condition is the result of a catecholamine-induced increasing of pulmonary capillary pressure and permeability as well as neutrophil accumulation and increased hydrostatic pressure due to overfilling or constriction of the pulmonary veins [35, 36].

63.2.1.8 Gastrointestinal, Nephrological, and Neurological Emergencies

Rarely, pheochromocytoma may present as gastrointestinal, nephrological, or neurological emergencies. In the former case, the cause may be an hemorrhage of the tumor with huge secretion of catecholamines leading to a hypertensive crisis associated with severe abdominal pain and vomiting. Alternatively, a prolonged exposure to high level of catecholamines may determine vasoconstriction of mesenterial arteries, which results in bowel ischemia requiring emergency surgery [2, 37].

Moreover, acute renal failure may be the result of rhabdomyolysis followed by myoglobinuric renal failure caused by extreme vasoconstriction related to an elevated levels of catecholamines [38].

Finally, most of the neurological symptoms caused by pheochromocytoma are the result of cerebral hemorrhage due to paroxysmal attacks of hypertension [2, 39].

63.2.2 Tests

63.2.2.1 Biochemical Tests

The diagnosis of pheochromocytoma depends crucially on the demonstration of excessive production of catecholamines. Currently, the diagnosis is established by elevated plasma metanephrines or elevated 24-h urinary metanephrines. Exception to this are tumors smaller than 1 cm which do not release catecholamines and the exceptional cases of tumors that purely produce dopamine [40, 41].

Notably, it is well known that, on the contrast of catecholamine which is secreted episodically and has a relatively short half-life, their O-methylated metabolites are produced continuously within tumor cells and have relatively longer plasma half-lives, making metanephrines more reliable for the diagnosis of pheochromocytoma [42, 43].

Important to keep in mind that when measuring the 24 h urinary excretion of metanephrines, urinary creatinine should be measured to verify the completeness of the urine collection. Regarding the assay of plasma metanephrines, it should be performed with the patient recumbent for at least 30–40 min and this test helps to differentiate neurogenic from hypertension caused by pheochromocytoma.. A value of plasma metanephrines of more than fourfold above the upper reference limit is reported to be associated with close to 100% probability of the tumor [44]. On

the other hand, in patients with plasma metanephrine values above the upper reference limit and less than fourfold above that limit, the clonidine suppression test combined may be useful [44]. In particular, a clonidine suppression test that does not suppress the elevated plasma normetanephrine levels to <40% after 3 h of administration has a very high sensitivity and specificity (100% and 96%, respectively) for diagnosing pheochromocytoma [40, 45].

Moreover, when a biochemical test is going to be performed, caffeinated beverages, strenuous physical activity, and smoking must be avoided at least about 8–12 h before the testing [46]. Likewise, some medications, such as isoproterenol, methyldopa, levodopa, tricyclic antidepressants, sympathomimetics, phenoxybenzamine, labetalol, acetaminophen, monoamine-oxidase inhibitors, beta-adrenergic blocking agents, calcium channel blockers, which are reported to interfere with assays of plasma and urinary metanephrines, should be discontinued at least 1 week before tests [40, 41].

Anyway, one clinical dilemma is whether to measure catecholamines metabolites in the blood or in a 24 h urine collection. Lenders et al. performed a multicenter study in 2002 and concluded that plasma-free metanephrines constitute the best test for excluding or confirming pheochromocytoma and should be the test of first choice for diagnosis of the tumor. They reported that a negative test result virtually excludes pheochromocytoma [42]. Moreover, the high diagnostic accuracy of measurements of plasma-free metanephrines has been confirmed by several independent studies [47–49]. On the other hand, Perry et al. reported that measurements of urine fractionated metanephrines by mass spectrometry provide excellent sensitivity (97%) and specificity (91%) for the diagnosis of PPGL [50].

All in all, the Clinical Practical Guidelines of Pheochromocytoma and Paraganglioma does not recommend that one test is superior to the other and concluded only that the initial biochemical testing for PPGL should include measurements of plasma-free metanephrines or urinary fractionated metanephrines [51].

63.2.2.2 Imaging Studies

Anatomic localization of a catecholamine-secreting tumor should be performed only after a biochemical diagnosis has been confirmed. Computer tomography (CT) is considered the gold standard imaging modality due to its excellent spatial resolution for thorax, abdomen, and pelvis [51]. CT is characterized by high sensitivity (88–100%) for the diagnosis of pheochromocytoma, although it decreases to approximately 90% in the case of paraganglioma [51, 52]. Anyway, CT lacks specificity, since pheochromocytoma may be either homogeneous and heterogeneous, solid, cystic, and necrotic with calcifications [51].

MRI, on the other hand, provides superior contrasting effects in soft tissues and therefore may be better for differentiating pheochromocytomas from adrenal adenomas. Moreover, it provides a better evaluation of the relationship between the tumor and the surrounding tissues, resulting in great support to exclude or confirm vessel invasion. Furthermore, iodide contrast agent is not necessary and the method does not use radiation: this makes MRI preferred in case of pregnant women and children [53]. Clinical Guidelines recommend MRI in patients with metastatic PPGLs, for detection of the skull base and neck paragangliomas, in patients with an allergy to CT contrast, and when radiation exposure should be limited [51].

Complementary to a CT scan or MRI, 123I-MIBG scintigraphy is a highly specific method. 123I-MIBG is administered intravenously and body scans are performed after 4 and 24 h. The main purpose of 123I-MIBG scintigraphy is to functionally confirm tumor tissue that has been localized via CT scan or MRI. It resulted also helpful to diagnose extra-adrenal pheochromocytomas and remaining tumor tissue after surgery. The specificity of this method is very high (95–100%); however, its sensitivity is significantly lower (77–90%) [6, 53].

Differential Diagnosis

As stated above, pheochromocytoma has been labeled "*the great masquerader*" for the wide spectrum of possible presentations which may mimic other more common clinical conditions.

Pheochromocytoma should be taken into consideration in cases of unexplained shock, especially when abdominal pain and pulmonary edema are associated. Likewise, pheochromocytoma should be considered in case of multiple organ failure, high fever, encephalopathy, and severe hypertension or hypotension. Moreover, consumption of certain illegal substances, such as amphetamine, cocaine, and lysergic acid, as well as some cardiological (arrhythmias such as paroxysmal supraventricular tachycardia, essential or renovascular hypertension) or psychological (anxiety disorders) conditions may cause manifestations mimicking pheochromocytoma [10].

Besides, worthy to be underlined that many types of stress can also significantly elevate concentrations of plasma and urinary catecholamines and their metabolites, but rarely they reach the levels typical of pheochromocytoma [10].

Physicians must forever recall that pheochromocytoma wears many disguises. The first step to obtain a correct diagnosis of pheochromocytoma is *think to pheochromocytoma*!

63.3 Treatment

63.3.1 Preoperative Management

Management of PPGL emergencies results directly correlated to symptoms and clinical presentation of the patient. Nevertheless, either it matters of an elective or emergency situation, administration of preoperative nonselective alpha-adrenoreceptor blockers (phenoxybenzamine) or alpha-1-selective adrenoreceptors blockers (doxazosin, prazosin, and terazosin) is recommended for all patients affected by hormonally functional PPGLs to prevent perioperative cardiovascular complications [51]. Anyhow, although performed by most of Institutions, to date, randomized controlled trials to support the use of pre-operative alpha-blockade are lacking and successful removal of PPGL has been reported without preparation of the patient with alpha-adrenergic blockade [54–56]. As second-line therapy, if the patient's blood pressure cannot be controlled with the alpha-adrenoreceptors blockade alone, additional calcium channel blocker can be administered. Besides, calcium channel blocker can be used in monotherapy in patients with normotensive or mild hypertension [57].

Moreover, if the heart rate is above 100 bpm 3–4 days after alpha-blockade is introduced, beta-adrenoreceptor blockers (such as propranolol or atenolol) should be administered to control tachycardia. It is crucial to keep in mind that the use of beta-adrenoreceptor blockers without therapy with alpha-adrenoreceptor blockers is contraindicated due to the risk of hypertensive crises caused by the unopposed stimulation of alpha-adrenergic receptors [51, 58]. Practical guidelines recommend preoperative medical treatment for 7–14 days to allow adequate time to normalize blood pressure and heart rate [51].

Further, the alpha-adrenergic blockade should be accompanied by a high-dose sodium diet (5000 mg/day) and adequate daily fluid intake (2.5 L/day) to prevent severe hypotension after tumor removal. Alternatively, patients should receive 1–2 L of intravenous saline (0.9% NaCl) solution one day before the surgery [51, 58]. Expanding the blood volume helps to mitigate or even avoid hypotension once the adrenergic stimulus has been removed in the postoperative period, although only retrospective data exist to support the practice [59].

The aim of the preoperative medical preparation in patients who request adrenalectomy for a PPGL should be to keep the blood pressure below 130/80 mmHg while sitting and not lower than 80/45 mmHg while standing. The target in the

heart rate is 60–70 bpm while sitting and 70–80 bpm while standing [59].

Metyrosine is a catecholamine synthesis inhibitor, which may be reserved in combination with alpha-adrenergic receptor blockers in case of refractory hypertension [57]. Anyway, many experts do not recommend Metyrosine due to its potential negative effects on cardiac function. Moreover, it is associated with several side effects, such as sedation, depression, and extrapyramidal manifestations [11].

Patients who present with PPGL crisis should be admitted to hospital for aggressive medical management of symptoms before surgical treatment [57]. In these cases, immediate surgical intervention without stabilization of vital parameters is associated with high morbidity and mortality. Although many of these patients can be stabilized by means of alpha-adrenoreceptors blockers, a multidisciplinary approach is required. Occasionally, intra-aortic balloon pump (IABP) or extracorporeal membrane oxygenation (ECMO) may be required to manage severe cardiogenic shock [23, 60].

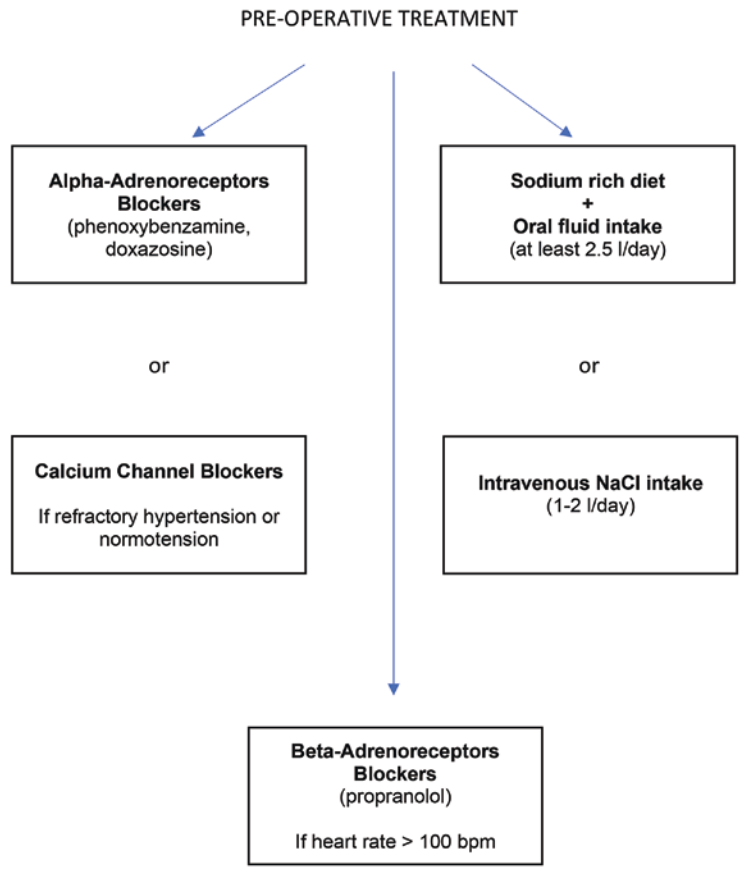
Overall, adrenalectomy can be performed within 1–2 weeks in patients who generally recover with medical and intensive care support. However, emergency surgery may be necessary in rare case of tumor rupture or uncontrolled bleeding [58].

The recommended pre-operative protocol is summarized in Flowchart 63.1.

63.3.2 Intra-Operative Management

It is crucial to achieve a successful treatment that the surgical and anesthesiologic team collaborate during the operation. The manipulation of the tumor may lead to an increase of the blood pressure or heart rate and surgeons may be asked to stop the surgical action to restore the vital parameters within the limits. Esmolol is usually administered in case of intra-operative hypertension;

Flowchart 63.1 Preoperative management



moreover, intravenous magnesium sulfate can be used to manage refractory hypertension [58].

Once the tumor has been removed, hypotension may occur: administration of intravenous isotonic fluid (0.9% NaCl) may help to face this situation. Besides, bolus or infusion of ephedrine or phenylephrine can be administered if needed [58].

63.3.3 Medical Treatment

Rupture of an adrenal pheochromocytoma is extremely rare and can be fatal due to sudden cardiovascular consequences with high mortality rate [61]. The exact mechanism of pheochromocytoma rupture is debated, but high blood pressure attributable to a massive release of catecholamines into the bloodstream is likely associated with vasoconstriction within the tumor and subsequent hemorrhage and necrosis. Furthermore, rapid tumor growth may play a role to determine high intracapsular pressure, which may lead to capsular tear and retroperitoneal bleeding [62].

In case of failure of medical conservative management and hemodynamic instability, transarterial embolization has been reported to be a viable option in case of pheochromocytoma rupture. Although emergency adrenalectomy for ruptured pheochromocytoma has been associated with a high mortality rate, endearing outcomes have been reported for cases in which transarterial embolization was used for hemostasis and patient stabilization until elective surgery can be performed [63–66].

63.3.4 Surgical Treatment

As stated above, emergency surgery in case of acute adrenal conditions is not recommended except for very selective cases. First of all, an extraordinary effort should be performed to stabilize the patient by means of medical management; surgery can be safely performed within 1–2 weeks after the patient's recovery [24].

Laparoscopic removal of pheochromocytomas and paragangliomas is worldwide considered the "gold standard technique" due to its high reproducibility associated with low postoperative morbidity, short hospital stay and operative time, fast postsurgical recovery, and high patient satisfaction [51].

Since the era of open adrenalectomy, the dogma has always been to ligate the adrenal vein as early as possible to prevent catecholamine surges related to gland manipulation (Fig. 63.1). Notwithstanding the rule "*the vein first*" is still followed in several institutions, recent studies reported that delayed adrenal vein ligation is safe and effective [67].

Although the trans-peritoneal approach is the most commonly used technique to remove pheochromocytoma, the retroperitoneoscopic route, popularized by MK Walz and his team, is progressively gaining more and more consensus [68]. Besides, a cortical-sparing surgery is considered suitable in the case of hereditary or bilateral pheochromocytoma to prevent postsurgical adrenal failure [51].

Finally, practical guidelines recommend open resection for large (more than 6 cm in diameter) or invasive lesions, as well as for pheochromocytoma with suspicion of malignancy [51].

63.3.5 Prognosis

Patients presenting with pheochromocytoma crisis suffer from a mortality rate approximately of 15% [69]. About 25% of patients remain hyper-

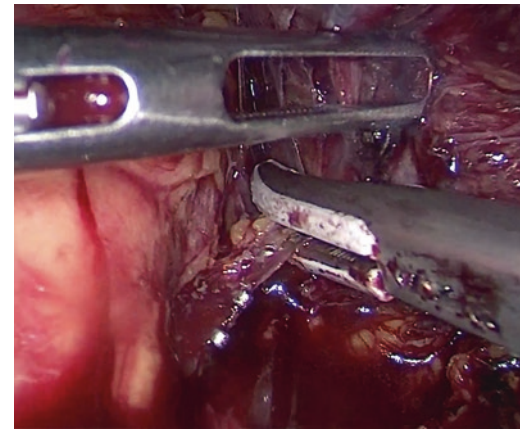


Fig. 63.1 The middle adrenal vein is ligated as early as possible

tensive following adrenalectomy: this may be due to coexisting essential hypertension or rarely to tumor relapse. Five-year survival for patients with benign pheochromocytoma is 95%, but varies from 36% to 50% in the case of malignant tumors [10].

Dos and Don'ts

- Emergency surgery in case of pheochromocytoma crisis is not recommended.
- Administration of alpha-adrenoreceptor blockers (eventually associated with beta-adrenoreceptor blockers) is recommended for all hormonally functional pheochromocytoma.
- The use of beta-adrenoreceptor blocker without alpha-adrenoreceptor blockers is not indicated and may lead to a hypertensive crisis.

Take-Home Messages

- Pheochromocytoma emergencies are rare but harbor high morbidity and mortality.
- A multidisciplinary evaluation is crucial for the management of adrenal emergencies related to pheochromocytoma.
- It is of paramount importance effort to obtain hemodynamic stability.
- The use of alpha-adrenoreceptor blockers is recommended before surgery.
- Adrenalectomy can be performed within 1–2 weeks in patients who generally recover with medical and intensive care support.

Multiple Choice Questions

1. Which is the main difference between pheochromocytoma and paraganglioma?
   A. The former is located inside the adrenal gland, the latter outside the adrenal gland (X)
   B. The former is located outside the adrenal gland, the latter inside the adrenal gland
   C. The former produces catecholamines, the latter glucocorticoids
   D. The former produces catecholamines, the latter sexual hormones
2. Pheochromocytoma may occur in a familial context. Which are the main associated syndromes?
   A. MEN I, MEN 2B, VHL syndrome
   B. MEN IIA, VHL syndrome, NF I (X)
   C. Conn Disease, MEN II B, NF II
   D. Cushing disease, MEN IIA, VHL syndrome
3. Which is the most common clinical presentation of PPGL?
   A. Headache, sweating, palpitations (X)
   B. Hypertensive crisis
   C. Multisystemic failure
   D. Acute abdomen
4. Which of the following actions may spring a pheochromocytoma crisis?
   A. Manipulation during surgery
   B. Trauma
   C. Administration of some medications (such as tricyclic antidepressants, levodopa, labetalol)
   D. All the above-mentioned answers (X)

5. What is the main cause of the complications of PPGL?
   A. Mass-effect
   B. Rupture
   C. Tumor necrosis
   D. High levels of circulating catecholamines (X)
6. Which is the first level test for a proper diagnosis of pheochromocytoma?
   A. CT scan
   B. US scan
   C. MRI scan
   D. Biochemical test (serum or 24-h urinary metanephrines level) (X)
7. Which is the best imaging study to localize pheochromocytoma?
   A. US scan
   B. CT scan (X)
   C. MRI scan
   D. 123I-MIBG scintigraphy
8. Which is the optimal pre-operative treatment of PPGL?
   A. Alpha-adrenoreceptor blockers + intense hydration ± beta-adrenoreceptor blockers (X)
   B. Beta-adrenoreceptor blockers + intense hydration
   C. Alpha-adrenoreceptor blockers
   D. Calcium channel blockers + intense hydration ± beta-adrenoreceptor blockers
9. In case of emergency presentation of pheochromocytoma, which is the best management?
   A. Emergency surgery
   B. Medical therapy associated with intensive care to stabilize the patient (X)
   C. Trans-arterial embolization
   D. None of the above mentioned answers
10. Which is the gold standard technique for the adrenal removal?
   A. Laparoscopic adrenalectomy (transperitoneal or retroperitoneal) (X)
   B. Robotic adrenalectomy
   C. Open adrenalectomy
   D. Depends on the experience of the surgeon

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