Non-MEN Familial Endocrine Syndromes: Von Recklinghausen Disease, Von Hippel-Lindau Syndrome, Pheochromocytoma/ Paraganglioma

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Contents

A. L. Shifrin et al. (eds.), *Endocrine Surgery Comprehensive Board Exam Guide*,
https://doi.org/10.1007/978-3-030-84737-1_39

Case Presentation

A 27-year-old woman presented with intermittent abdominal pain over the last 2 years. The pain was localized to right lumbar region with no specific exacerbating or relieving factors. On questioning, she reported that the family physician had diagnosed hypertensive episodes, accompanied by intermittent attacks of severe flushing, perspiration, and ectopic heartbeat 3 years ago and that she is currently requiring more than three antihypertensive drugs for optimal control. Detailed physical examination revealed a blood pressure of 160/90 mmHg, heart rate between 100 and 110/min, multiple soft to firm nodular swellings over the entire body including the face, multiple brown macules, and generalized freckling of the skin. On ophthalmic examination, yellow-brown pigmentation on the iris was seen, and abdominal examination was unremarkable. Family history revealed similar nodular lesions in her mother and sister with no major illness in them or other family members. Ultrasonography of the abdomen revealed a mass lesion in the right adrenal gland, and CT scan showed a 4.6 × 3.8 cm mass arising from right adrenal gland. Her laboratory findings revealed that 24-h urinary metanephrines and normetanephrines were elevated. Investigations for neck pathologies including thyroid and parathyroid diseases were negative.

Questions

1. What is the most likely diagnosis?
   (a) Von Hippel-Lindau syndrome
   (b) Neurofibromatosis type 1
   (c) Addison's disease
   (d) Kallmann's syndrome
2. All of the following regions of the adrenal cortex and medulla with its producing hormones are given correctly *except*:
   (a) Zona glomerulosa – mineralocorticoids
   (b) Zona fasciculate – glucocorticoids
   (c) Zona reticularis – aldosterone
   (d) Medulla – epinephrine and norepinephrine
3. Neural crest cells migrate to the adrenal glands to form which region?
   (a) Zona glomerulosa
   (b) Zona fasciculate
   (c) Zona reticularis
   (d) Medulla
4. Which is the secretory cell found in the adrenal medulla?
   (a) Chromaffin cells
   (b) Neuroglial cells
   (c) Follicle cells
   (d) Oxyphil cells

5. Pheochromocytoma can secrete excess amounts of all of the following *except*:
   (a) Cortisol
   (b) Dopamine
   (c) Norepinephrine
   (d) Epinephrine
6. Which of the following imaging technique is important whether the malignant form of the tumor can be treated with lutetium?
   (a) Computed tomography (CT) scan
   (b) Magnetic resonance imaging (MRI) scan
   (c) Metaiodobenzylguanidine (MIBG) scan
   (d) Ga-DOTATATE PET/CT
7. The preoperative preparation of a patient with pheochromocytoma should include all of the following *except*:
   (a) An alpha-adrenergic blocker such as phentolamine
   (b) A beta-adrenergic blocker such as propranolol
   (c) Intravenous hydration to avoid volume depletion
   (d) Systemic steroids to adrenal insufficiency
8. Which familial endocrine syndrome and the related gene is given correctly?
   (a) Von Hippel-Lindau syndrome – PTEN
   (b) Neurofibromatosis type – neurofibromin gene
   (c) Von Recklinghausen disease – SDHx genes
   (d) Hereditary paraganglioma – VHL tumor suppressor gene

Open-Ended Oral Exam Questions

1. Please define hereditary endocrine syndromes affecting the adrenal glands.
2. Please define the affected organs and characteristic lesions in patient with von Hippel-Lindau syndrome.
3. Please define the short-term and long-term stress response for adrenal hormones.
4. What are the three regions of the adrenal cortex and what hormones do they produce?

39.1 Hereditary Pheochromocytoma and Paraganglioma

39.1.1 Introduction

Rare neuroendocrine tumors, pheochromocytomas and paragangliomas, also known as extra-adrenal pheochromocytomas, originate from neural crest cells of the autonomic nervous system. In a significant proportion of hereditary pheochromocytomas, the gene mainly responsible for the origin of these tumors relates to genetic control of succinate dehydrogenase (SDH) [1, 2].

In relation to the autonomic nervous system, it has been reported that the organ of Zuckerkandl and the adrenal medulla are related to the sympathetic paraganglia, while the carotid bodies are related to the parasympathetic paraganglia. The WHO defined pheochromocytoma in 2004 as "tumors derived from neural crest origin chromaffin cells which arise in the adrenal medulla." While tumors from neural crest cells that arise from the adrenal medulla are called pheochromocytomas, those that arise extra-adrenally are referred to as paragangliomas [3].

Pheochromocytomas display a relatively less malignant (10%) pattern when compared to paragangliomas. Paragangliomas are found mostly in the abdomen, in which case they have proven to be 15–35% more malignant when compared to the other regions in which they can be found. The paragangliomas can also be found in the head and neck region, where they tend to be painless masses which are vertically fixed but laterally mobile, a characteristic termed Fontaine's sign [4].

39.1.2 Epidemiology and Genetics

Historically, pheochromocytoma was referred to as the 10% tumor because it was regarded as 10% malignant, 10% familial, 10% extra-adrenal, and 10% bilateral. Currently, however, both paragangliomas and pheochromocytomas are actually considered to be 30% hereditary [5]. Pheochromocytomas are considered rare tumors as the incidence of these tumors is 2–9.1 per million among adults per year [6]. Men and women are equally at risk of developing these tumors, but paragangliomas and pheochromocytomas tend not to be present in the pediatric populations [6]. However, when these syndromes do occur in pediatric patients, they are usually hereditary and multifocal in nature.

There is variety among the familial genetic syndromes related to paragangliomas and pheochromocytomas [7]. Such an example is the result of a mutation on chromosome 3 at a tumor suppressor gene that causes the autosomal dominant VHL syndrome, which has an estimated prevalence of 1/35,000.

The syndrome can affect the eyes, brain, pancreas, ears, adrenal glands (causing pheochromocytomas in 20–80% of VHL patients), and prostate. Another example is the *SDHx* gene mutations which were found to be related to familial paragangliomas [8]. A chronic hypoxic signal is produced in the mitochondrial II complex due to these mutations which causes cellular proliferation [9]. There is an association between the familial paragangliomas of the abdomen or thorax that are likely to be malignant with the *SDHB* gene and those of the head and neck which are less likely to be malignant with *SDHD* subunits, which are both located on chromosome 1. Both of the subunits have a weak association with pheochromocytoma [8]. However, paragangliomas of the head and neck region are diagnosed later in life than pheochromocytomas. This is in part due to the catecholamine-associated symptoms in pheochromocytomas [10]. The hereditary tendency of *SDHx* genes is autosomal dominant. It should be noted that the *SDHD* gene, if transmitted maternally, exhibits a carrier state without affecting the phenotype [11]. Paragangliomas and pheochromocytomas can be associated also with tuberous sclerosis, ataxia-telangiectasia, Sturge-Weber, and Carney complex [12].

39.1.3 Clinical Presentation

Pheochromocytoma and paraganglioma patients usually suffer from hypertension that can be episodic, new onset, and refractory or persistent despite standard pharmacological agents. In addition to hypertension, patients can exhibit signs and symptoms such as palpitations, headaches, and diaphoresis. Some other manifestations of these patients include tremor, anxiety, pallor, tachycardia, flushing, visual disturbances, orthostatic hypotension, fever, heat intolerance, abdominal pain, vomiting, constipation, hematuria (due to a bladder paraganglioma), polyuria, hyperglycemia, polydipsia, and hypercalcemia [13]. On the other hand, because pheochromocytomas tend to have cystic degeneration, even if the tumor reaches extreme sizes, some patients can be asymptomatic. While these lesions are generally benign, pheochromocytomas may be malignant from 5% to 10%, and paragangliomas may be malignant from 15% to 35% [14]. Malignant tumors that produce catecholamines are present clinically with symptoms identical to those of their benign counterparts. Upon metastasis, the tumors spread mostly to the regional lymph nodes, liver, bone, and lung [15].

39.1.4 Diagnosis and Indications for Surgery

The workup of suspected pheochromocytoma or paraganglioma includes initial biochemical screening. Diagnosis is imperative, as lack of identification of these syndromes may

lead to stroke or even sudden death. Recognition of the excessive production of catecholamines is the first part of the informed evaluation. Comorbidities, such as severe congestive heart failure, acute MI, acute alcohol withdrawal, acute clonidine withdrawal, emotional or physical stress, subarachnoid hemorrhage, or cerebral tumors causing comatose state, and interfering substances, in particular levodopa, amphetamines, pseudoephedrine, dietary caffeic acid, acetaminophen, reserpine, prochlorperazine, ethanol, labetalol, methylglucamine of contrast media with iodine, and mostly tricyclic antidepressants and phenoxybenzamine, are all important factors that have to be taken into account. If the blood and urine analyses indicate different results, then the clonidine suppression test is used to make a distinction between essential hypertension and pheochromocytoma. Essential hypertension is indicated if there is more than 50% suppression, and no suppression suggests that the patient has pheochromocytoma.

Regarding the catecholamines produced, while pheochromocytomas secrete epinephrine, paragangliomas secrete norepinephrine. Moreover, it should be noted that norepinephrine is produced in excess in VHL-associated tumors, whereas both epinephrine and norepinephrine are produced in MEN 2-associated tumors. Dopamine is secreted in malignancy due to alterations in catecholamine synthesis. Since pheochromocytomas and paragangliomas are neuroendocrine tumors, serum chromogranin A can be used as a biomarker for identification [16]. It is important to keep in mind that measurement of serum chromogranin A may result in false positives in many instances including renal insufficiency patients.

39.1.5 Preoperative Management and Radiological Studies

Paragangliomas and pheochromocytomas are evaluated radiologically via CT, MRI, and MIBG scintigraphy [17]. Although CT is initially the preferred modality, its specificity is relatively poor, at 50% [17]. CT scans are recommended before and after the injection of IV contrast medium for evaluation of pheochromocytomas. If CT imaging excludes the presence of paragangliomas intra-abdominally, the head and neck region of the patient should also be examined for the possible presence of tumors at the carotid bodies and the mediastinum.

In cases which patients are ineligible for CT scans (e.g., pregnancy, allergy, pediatrics), MRI should be preferred instead. Due to increased vascularity around the paragangliomas and pheochromocytomas, T2-weighted images show increased signal intensity. Signal intensity on T2 can be diminished if the tumor is large enough to be associated with hemorrhaging or necrosis. MRI has a higher specificity (50–100%) and higher sensitivity (90–100%) when compared to CT. If biochemi-

cal testing suggests the presence of pheochromocytoma in a patient, but a CT scan contradicts the results, then MRI can be used for additional investigation [12].

Surgical intervention to remove pheochromocytoma and paraganglioma in a patient is the preferred treatment route among several other options. Because the tumors are highly vascular, upon diagnosis of pheochromocytoma or paraganglioma, patients should never have a FNAB that may potentially cause hemorrhage, hypertensive crisis, or even death. In general, α-blockade is recommended to be administered at least 2 weeks preoperatively, in particular phenoxybenzamine. If the patient has tachycardia, β-blockade ought to be added to the ongoing treatment. Preoperative treatment must continue up to the morning of the operation. Blood pressure alterations are anticipated during the operation. Therefore, the patient must be monitored hemodynamically and have an optimal IV access for serious changes. Norepinephrine may need to be added to the postoperative treatment for routine monitoring and maintenance of blood pressure.

Genetic counseling should be offered to those with a positive or suspected family history of pheochromocytoma or paragangliomas. If a patient is 50 years old or younger with a positive family history, possible *VHL, SDHB, SDHD*, and *RET* mutations must be tested.

39.1.6 Surgical Techniques

The gold standard surgical intervention for pheochromocytoma patients is minimally invasive (either laparoscopic or retroperitoneoscopic) adrenalectomy, along with cortical-sparing adrenalectomy which is especially important for cases with hereditary disease and a high risk for bilateral pheochromocytoma [18]. Even though data for robotic adrenalectomy is scarce, the technique is widely accepted among surgeons [19]. Several studies conducted in order to compare laparoscopic and robotic surgeries failed to show a statistically significant difference in perioperative outcomes [19]. Surgical technique should be chosen based on patient demographics, tumor features, and most importantly the surgeon's experience [19]. Intraoperatively, in order to evaluate real-time hemodynamic volatility, invasive blood pressure monitoring must be done. Esmolol or sodium nitroprusside (short-acting vasodilators) are best for optimal hypertension control [18].

Many elements factor into the decision of radical or conservative adrenalectomy in pheochromocytoma patients. Due to the risk of recurrence or residual disease, unilateral total adrenalectomy is preferred in patients with sporadic occurrence. However, in young patients with hereditary pheochromocytomas due to germline mutations, the tumors can present

bilaterally, which can call for the removal of both of the adrenal glands [20]. However, resection of both adrenal glands can lead to unwanted complications since the patients will be dependent on long-term supplementation of glucocorticoid, affecting patient quality of life [21]. Patients can avoid these complications by opting to "cortex-sparing" surgery, benefitting from the remaining adrenal cortex, as deemed appropriate [22]. It should also be considered that those patients that present with hereditary pheochromocytomas tend to have benign tumors. Even when the adrenal medulla is left in situ, postoperative ipsilateral recurrence rates of 3–7% have been reported after a median interval 8–10 years [23, 24]. Therefore, all aspects of the extent of surgery should be considered carefully to improve clinical outcome and quality of life of the patients.

For familial paragangliomas, surgical resection – if possible – remains the only choice of curative treatment. However, due to the multifocal nature of paragangliomas, the morbidity of the operation may necessitate alternative treatments to the surgical intervention (e.g., radiotherapy, active surveillance) [25]. Without proper treatment compliance, patients with an *SDHB* germline mutation that have had a unilateral adrenalectomy carry the risk of going through an adrenal crisis. Usually, adrenal-sparing surgery would not be considered for those patients with *SDHB* mutations due to the advanced nature of the disease, and total adrenalectomy would be favored in these patients to avoid preventable metastasis. But, in situations in which patients are disregarding their condition and run the risk of adrenal crisis, the risk of metastasis may be overlooked in relation to the risk of adrenal crisis, and cortex-sparing adrenalectomy may be advantageous [24].

39.1.7 Postoperative Follow-Up and Prognosis

Due to the possibility of recurrence of paragangliomas and pheochromocytomas, patients –especially those with a hereditary history – ought to be followed up throughout their entire life. As the rate of recurrence for both pheochromocytomas and paragangliomas is hard to foretell, authors have investigated factors that correlate with the recurrence. Due to their more difficult resection, right-sided tumors have a higher risk of recurrence than their left counterparts. The prognosis for such patients is inconsistent; half have more than a 20-year life expectancy, whereas the other half suffer recurrence and disease progression within the first 1–3 years after the diagnosis. The probability of new event occurrence is higher in younger patients and also in those with hereditary and larger tumors than the sporadic and smaller tumors in elder patients [15].

39.2 Von Hippel-Lindau Syndrome

39.2.1 Introduction

Hippel-Lindau (VHL) is relatively rare (1 in 35,000 incidence ratio) autosomal dominant syndrome, caused by mutations in the *VHL* tumor suppressor gene located on chromosome 3p25-26. The mutation causes vascular endothelial growth factor (VEGF) upregulation. VHL is related to tumors in several organs such as the adrenal glands, kidneys, eyes, inner ears, CNS, pancreas, and epididymis [26]. The specific tumors related to VHL include pheochromocytoma, renal cell carcinoma (RCC), hemangioblastoma of the CNS, endolymphatic sac tumors, retinal angiomas, pancreatic cysts, and neuroendocrine tumors [26]. If a patient has a missense mutation, then this patient is classified as VHL type 2 and usually also has pheochromocytoma. If other mutations are present, the patient is classified as VHL type 1 [27].

39.2.2 Epidemiology and Genetics

One in 36,000 are born with VHL syndrome, which by the age of 65 has a 90% penetrance [28]. Historically, the median age of survival was less than 50 before CT alongside other imaging techniques, and screening methods for the affected individuals were developed. RCC or CNS hemangioblastoma was the cause of death in those individuals. With the development of the aforementioned diagnostic modalities, survival rates increased.

39.2.3 Clinical Presentation

VHL affects several organs such as the adrenal glands, eyes, pancreas, CNS, inner ears, and epididymis [26]. Even asymptomatic patients can be diagnosed by utilizing routine genetic tests and imaging techniques. Clinical diagnosis of pheochromocytoma is confirmed by a positive family history of VHL as well as positive test results indicating a diagnosis for pheochromocytoma, CNS hemangioblastoma, or renal manifestations. If the patient is diagnosed de novo, then she must meet the criteria of having a visceral tumor with one CNS manifestation or two or more CNS hemangioblastomas.

Clinical presentations of the affected organs aforementioned differ from each other. Therefore, they have been depicted in different groups below and will be further characterized: visceral lesions, CNS lesions, retina, and inner ear [29].

39.2.3.1 Visceral Lesions

Comorbidity of pheochromocytomas in VHL patients is 20% with a mean age of 30 years. Lesions can be bilateral as well as extra-adrenal paragangliomas.

Patients with VHL are more likely to develop both solid lesions of the kidneys and renal cystic disease – up to 25–45% – which can be multifocal and bilateral with the mean age of 39 years. Due to the possibility of malignancy of RCC, it is one of the most significant causes of death. If left untreated, 13–42% of the patients will have tumors that metastasize [27].

From 17% up to 56% of VHL patients with the comorbidity of pancreatic lesions will develop cystic lesions – serous cystadenomas – that can be single or multiple. Even if the lesions lack malignancy potential, they may occupy both the endocrine and exocrine portions of the pancreas, leading to insufficiency and obstruction of the intestine and bile duct. Always nonfunctional but potentially malignant, pancreatic neuroendocrine tumors (PNETs) can be seen in 12–17% of VHL patients. Even if PNETs become malignant, they are not a common cause of death [10].

39.2.3.2 CNS Lesions

Almost 80% of VHL patients, with a mean age of 33 years, suffer from hemangioblastomas which makes it the most common tumor in patients with VHL. They never cause malignancy, but depending on their size or location, hemangioblastomas can cause swelling and result in symptoms that correlate with their specific location along the craniospinal axis.

39.2.3.3 Retina

Up to 60% of the VHL patients – with a relatively early mean of age of 25 years – have retinal hemangioblastomas which can be both multifocal and bilateral. Even if the lesion is benign, it may cause vision loss [29].

39.2.3.4 Inner Ear

A less common manifestation of VHL patients is endolymphatic sac tumors that may lead to equilibrium disorders and hearing loss [29].

39.2.4 Diagnosis and Indications for Surgery

In order to determine gene rearrangements and deletions, complete gene sequencing methods are used to detect the germline mutations of VHL [26].

If a patient with VHL has a PNET, the tumor is always nonfunctional. This leads to a failure of detection of the tumor in biochemical screening tests. Plasma and 24-h urinary meta-

nephrine levels should be controlled before any intervention is carried out due to the possibility of overlooking a case of pheochromocytoma and risking a hypertensive crisis.

39.2.5 Preoperative Management and Radiological Studies

The gold standard for screening and follow-up of visceral lesions related to this disease is contrast-enhanced abdominal CT. This modality is preferred also due to its feasibility and accessibility. MRI can be used alternatively to the CT in the case of an allergy or similar constraints.

Biochemical analysis and radiological modalities are used together to identify adrenal masses. CT is used if the catecholamine levels are elevated. If the CT result is negative, then the nuclear MIBG scan is used to identify any extra-adrenal paragangliomas.

Preoperative management of the patients is complicated due to the involvement of multiple lesions in multiple organs. Thus, a team with individuals of multidisciplinary backgrounds such as neurosurgeons, endocrine surgeons, ophthalmologists, and urologists is needed to manage these syndromes.

39.2.6 Surgical Techniques

Surgical techniques employed for treatment depend on the clinical presentation of the VHL disease. When weighing options for extent of surgery in von Hippel-Lindau disease, in vitro studies have shown that genetic changes tend to be missense mutations rather than deletions or other kinds of mutations that would lead to a nonfunctional pVHL in pheochromocytomas [30, 31], though this does not necessarily mean that the possibility of recurrence can be excluded. Yet, it should be noted that these VHL-related chromaffin tumors have a relatively low malignancy rate as 1–5% [24, 32], making subtotal adrenalectomy a plausible alternative to the radical route, and has been executed successfully in both adults and children with VHL [33]. The clinical presentation of pheochromocytoma and paraganglioma is further discussed, and treatment options are considered in the previous chapter as either minimally invasive or robotic adrenalectomy.

The main treatment options for retinal hemangioblastomas are cryotherapy and laser photocoagulation. If retinal detachment occurs from traction and exudation, vitreoretinal surgery can be performed. Anti-VEGF therapy in the intravitreal compartment should be considered if the optic nerve is at risk due to its proximity with the hemangioblastoma [34].

Treatment of endolymphatic sac tumors calls for the surgical resection of the tumor as the gold standard. The resection may relieve hearing-related symptoms [34]. For RCC lesions less than 3 cm in diameter, surgical resection is advised. Total nephrectomy has been replaced by partial nephrectomy (nephron sparing). Also, radiofrequency ablation is an alternative technique used in addition to surgery in order to enhance results [34].

39.2.7 Postoperative Follow-Up and Prognosis

Gaps of 6–12 months are arranged between the CT imaging along with history taking and physical examinations in patients with renal lesions. Improvement of the quality of life of VHL patients is evident, thanks to the development of imaging modalities, cumulative clinical knowledge of such patients, and novel genetic techniques. Such improvements also contribute to better prognosis in these patients.

39.3 Neurofibromatosis Type 1 (Von Recklinghausen Disease)

39.3.1 Introduction

The autosomal disorder neurofibromatosis type 1 (NF-1) arises due to mutations at c17q11 in the *NF1* tumor suppressor gene which is a very large gene with several mutations identified. No correlation between phenotype and genotype has been found. Café au lait spots and benign cutaneous neurofibromas are the characteristic features. Some NF patients (less than 4%) tend to develop pheochromocytoma that is 10% bilateral and 10% malignant. Of the disease, 96% is intra-adrenal and may show a mixed pathology, such as ganglioneuroma and neuroblastoma. In NF-1, duodenal periampullary somatostatinomas with psammomatous calcification are almost pathognomonic. Rarely there may be associated HPT and MTC endocrine tumors [35].

39.3.2 Epidemiology and Genetics

Mutations on chromosome 17 at the tumor suppressor gene cause an autosomal dominant NF1 disease with a prevalence rate of 1/3000 people. Two percent of the NF1 patients have paragangliomas and pheochromocytomas, whereas 20–80% of VHL patients have paragangliomas and pheochromocyto-

mas [8]. A greater prevalence is estimated if there is a comorbidity with hypertension or duodenal carcinoids [35].

39.3.3 Clinical Presentation

The patients may be found to have café au lait macules, bone lesions, optic glioma, several types of neurofibromas, Lisch nodules, freckles in areas of opposing skin such as the axilla or inguinal area, pheochromocytoma, and paraganglioma.

Café au lait macules are well-defined and regular macules with hyperpigmentation in their typical forms. If they are atypical, they exhibit an irregular border and a heterogenic pigmentation [36]. The aforementioned osseous lesions can be listed as osteoporosis, osteopenia, scoliosis, pseudoarthrosis, and sphenoid wing dysplasia. As scoliosis patients have a 21–49% likelihood of having comorbidity with the NF-1 disease, the pediatric routine clinical examination must be executed carefully. The evaluation must take into consideration the potential of a patient having NF-1 symptoms [36]. The NF-1-associated pheochromocytomas and paragangliomas are diagnosed at similar ages compared to the sporadic counterparts [37]. The NF-1-associated pheochromocytomas and paragangliomas tend to be active biochemically, MIBG-positive, and unilateral [37].

39.3.4 Diagnosis and Indications for Surgery

The diagnostic criteria of NF-1 according to the National Institutes of Health (NIH) are met if two or more of these symptoms are seen [36]:

1. Six or more café au lait macules that are larger than 15 mm in diameter in postpubertal patients and macules larger than 5 mm in diameter in prepubertal patients
2. A distinguishable osseous lesion
3. Optic glioma
4. Two or more of any type of neurofibromas or one plexiform neurofibroma
5. Two or more Lisch nodules
6. Axillary or inguinal freckles
7. Positive first-degree family history

39.3.5 Preoperative Management and Radiological Studies

The main aim of preoperative management is to identify potentially treatable symptoms and complications. The types of neurofibromas can differ from spinal nerve root, nodular or dif-

fuse plexiform, dermal, or neurofibromatous neuropathy. The management of dental neurofibromatosis mostly involves surgical intervention. Alternatively, laser ablation, emollients, electrodessication, psychological support, or camouflage makeup may be used.

More than half of NF-1 patients also have internal tumors which can be evaluated by the volumetric whole-body MRI modality to observe their tumor growth and burden characteristics.

Recent studies conducted in mice models showed that imatinib, mTOR inhibitors, and selective MEK inhibitor therapies resulted in tumor size reduction [38].

Due to the possible peri–/postoperative complications of the cardiovascular system such as cardiovascular crisis, screening with plasma or urine free fractionated metanephrine levels should be done before any surgical intervention [37].

39.3.6 Surgical Techniques

NF-1 patients are monitored via active surveillance without the application of any medical or surgical treatments. Yet, some particular cases need such treatment [39]. Radiotherapy provides only a local and symptomatic treatment of NF-1 and does not contribute to the overall survival of the patients according to retrospective studies. Due to the increased risk of secondary malignancy in plexiform neurofibroma, radiotherapy should be avoided specifically in this situation. Thus, surgical intervention along with medical treatments can be used, when necessary [39].

Surgical intervention is comprised of surgical resection, laser treatment, and orthopedic surgery. Surgical resection can be favored in cutaneous and plexiform neurofibromas. Yet, recurrence is common in such resections. Approximately 10–25% of pheochromocytoma patients have NF1-related bilateral adrenal disease [40, 41]. Low occurrence of pheochromocytoma in NF1 patients makes it less suitable for subtotal adrenalectomy, yet when these adrenal neoplasms do develop, they tend to do so bilaterally. These could be regarded as pheochromocytoma-prone NF1 mutations, though further evaluations are needed to characterize this association. Although subtotal adrenalectomy may not be favored for an adrenal tumor on one side, the malignancy rates of adrenal neoplasms range between 1% and 7% [40, 42], and cortex-sparing surgery may be performed on the opposite gland if the tumor is bilateral. Malignant peripheral nerve sheath tumor is the main indication for surgical resection in NF-1 patients [39]. Moreover, if the freckles and café au lait macules affect the quality of life of a patient, laser removal can be considered. Orthopedic surgeries can be carried out in order to correct osseous lesions [39].

39.3.7 Postoperative Follow-Up and Prognosis

NF-1 patients have the highest Clavien-Dindo graded complication rates for pheochromocytoma or paraganglioma as compared to those arising in MEN 2 and VHL, and among these three hereditary types of pheochromocytomas and paragangliomas, NF-1 patients also have the most intraoperative hemodynamic volatility [43].

Answers

1. (b); 2. (c); 3. (d); 4. (a); 5. (a); 6. (d); 7. (d); 8. (b)

Answers to Open-Ended Oral Exam Questions

1. MEN 2A, MEN 2B, MEN 4, von Hippel-Lindau syndrome, Neurofibromatosis type I, hereditary pheochromocytoma/paraganglioma
2. VHL affects several organs such as the adrenal glands, eyes, pancreas, CNS, inner ears, and epididymis. Clinical presentations of the affected organs have been depicted in different groups as follows and will be further characterized: visceral lesions, CNS lesions, retina, and inner ear.
3. The short-term stress response involves the hormones epinephrine and norepinephrine, which work to increase the oxygen supply to organs important for extreme muscular action such as the brain, lungs, and muscles. In the long-term stress response, the hormone cortisol is involved in catabolism of glycogen stores, proteins, and triglycerides, glucose and ketone synthesis, and downregulation of the immune system.
4. The regions from the most outer layer are the zona glomerulosa, the zona fasciculate, and the zona reticularis which produces aldosterone and glucocorticoids such as cortisol and androgens, respectively.

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