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CASE REPORT

Anesthetic management of a patient with type 1 neurofibromatosis and an occult pheochromocytoma: a case report

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Abstract Neurofibromatosis type 1 is a complex genetic disorder affecting multiple organ systems. Cardiovascular manifestations include hypertension, often associated with concomitant pheochromocytoma. We present a hypertensive crisis during induction of anesthesia in a patient with neurofibromatosis type 1, scheduled for abdominal myomectomy, which revealed an undiagnosed pheochromocytoma. The case highlights the importance of assessing all patients with neurofibromatosis type 1 for pheochromocytoma, because if it is left undiagnosed, it can be disastrous in the setting of anesthesia and surgery.

Introduction

Neurofibromatosis type 1 (NF-1) is a complex multi-systemic genetic disorder associated with the mutation of a gene on chromosome 17. The changes on the neurofibromin protein provoke widespread effects on ectodermal and mesodermal tissue, with the formation of tumors primarily on the nervous system and the skin.[1,2] It is an autosomal dominant disorder with complete penetrance, meaning that all the patients with the disorder will have some phenotypic expression during their lifetime, though the severity and the manifestations vary significantly among individuals. Neurofibromas are the characteristic lesions of the condition and occur not only in the neuraxis but also at the cardiovascular, the respiratory, the genitourinary system, and the gastrointestinal tract. Therefore, it is of crucial importance for the anesthetist to pay attention to the proper evaluation of such patients. The cardiovascular manifestations of NF-1 include hypertension, which may be associated with renal artery stenosis or pheochromocytoma.[1] The occurrence of pheochromocytoma in NF-1 varies from 1% to 5.7%. It is

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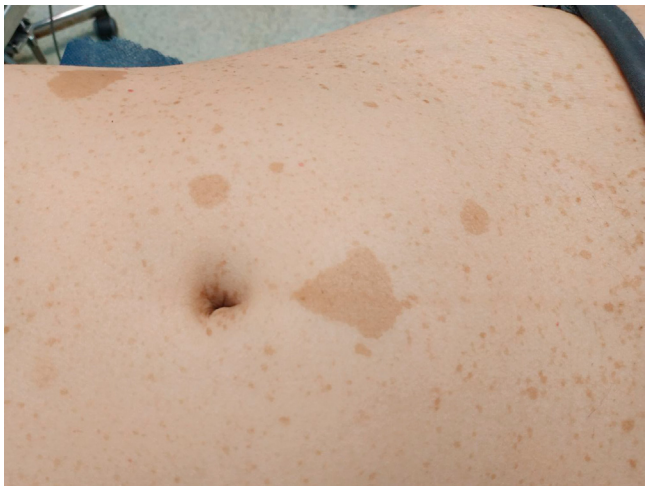

Figure 1 Patient's abdominal presence of ''cafe au lait'' spots.

a tumor originating from the adrenal medulla resulting in secondary hypertension. When undiagnosed, it is associated with very high mortality. Approval and written informed consent were received from the patient.

Case report

A 42-year- old white female patient was admitted to the OB/GYN department due to an episode of loss of consciousness related to anemia. The patient's height was 1.55 cm, and she weighed 58 kg. Despite receiving ferrum and folic acid supplements during the previous months, her hemoglobin was no higher than 6.5 $g.dL^{-1}$. Through emergency ultrasound and lower abdominal MRI assessment, a uterine fibroid was found, and the patient was scheduled for open myomectomy the following day.

She had a history of type 1 neurofibromatosis firstly diagnosed in 1989 due to the appearance of ''café au lait'' spots (Fig. 1), and since then she had been under close surveillance. Physical examination revealed no further findings. Her Blood Pressure (BP) was: 140/70 mmHg, with a Heart Rate (HR) of 102 bpm. Results from laboratory examination were normal.

The evening before surgery the patient received in total 2 RBC and 1 FFP, which raised her hemoglobin at the level of 8.9 $g.dL^{-1}$.

There was no history of allergies, drug consumption, smoking, or alcohol abuse. She had previous surgeries: once for removal of a giant cell granuloma of the mandible in 1985, and twice for excision of ulnar nerves neurinomas, in 1990 and 2012. No complications during general anesthesia were mentioned. Her airway assessment was excellent with Mallampati I, good cervical mobility, and mouth opening.

Upon arrival at the operation room, standard monitoring that consisted of ECG 3-lead continuous recording, non-invasive blood pressure measurement and pulse oximetry was connected to the patient. Venous access with one 18G catheter and one 16G catheter were established. Her vital signs upon the beginning were the following: blood pressure of 180/100 mmHg, heart rate of 110 bpm, and SpO_2 of 99%. Administration of 2 mg of midazolam and 100 mcg of fentanyl for anxiolysis and sedation did not have any effect on blood pressure, and at that point the leading anesthetist started having concerns regarding proceeding with the operation. Invasive blood pressure measurement was established just before induction of anesthesia.

Table 1 Patient's Laboratory examination for pheocromocytoma.

	Patient's value	Normal value
24 h urine VMA	**7.5** mg/ 24 h	1.8–6.7
24 h urine metanephrine	223 μg/ 24 h	52–341
Plasma metanephrine	**108** $ng.L^{-1}$	< 86 $ng.L^{-1}$
Plasma normetanephrine	**436** $ng.L^{-1}$	< 133 $ng.L^{-1}$
3-methoxytyramine	< 5 $ng.L^{-1}$	<17 $ng.L^{-1}$

For the induction, 100 mcg of fentanyl, 20 mg of etomidate and 50 mg of rocuronium were administered intravenously. After drug administration and during bag-mask ventilation, her blood pressure raised further to 220/120 mmHg with a heart rate of 135 bpm. To exclude inadequate anesthesia, bolus doses of 50 mg propofol were given up to a total dose of 150 mg. A continuous Intravenous (IV) infusion of glyceryl trinitrate (250 $mcg.mL^{-1}$ solution) was started. At that point, the consultant anesthesiologist suspected a concomitant pheochromocytoma and a decision was made to refrain from performing the surgery and wait until the muscle relaxant wears off. A laryngeal LMA 4 was introduced, and anesthesia was maintained with a mixture of oxygen, nitrous oxide, and sevoflurane achieving a MAC of 0.8. Blood pressure was maintained at the level of 160–170/80–90 mmHg.

A peripheral nerve stimulator was used, and Train Of Four (TOF) test was performed to assess the depth of neuromuscular blockade. Sugammadex was administered (2 $mg.Kg^{-1}$) for neuromuscular blockade reversal. During extubation the blood pressure raised again at 220/110 mmHg, and the glyceryl trinitrate infusion was increased. The patient was extubated with a blood pressure of 150/80 mmHg and a heart rate of 80 bpm. Respiratory function, hemodynamic status, and pain scores were continuously evaluated. Blood pressure remained between 160–170/85–95 mmHg with a heart rate of 85–95 bpm. Surgery cancellation and extensive re-evaluation of the patient was decided by both the anesthetic team and the gynecologist.

Post-operatively, after endocrine and cardiac consultation, a series of exams were requested. The laboratory results are shown in Table 1.

Along with the extensive blood and urine analysis, CT and MRI of the retroperitoneal space were performed, showing a lesion of 2 cm on the left adrenal gland.

The patient was referred to an endocrine surgery department where the diagnosis of pheochromocytoma was made. Preparation for surgery consisted of a-blockade with phenoxybenzamine followed by b-blockade and subsequently the resection of the tumor. The pathology examination of the resected tumor contained all the morphological characteristics ([+] chromogranin, Ki67 positive cells < 1%) that render the diagnosis of pheochromocytoma final.

Discussion

We hereby present a patient with type 1 neurofibromatosis, presenting for myomectomy, who developed hypertensive crisis during induction of anesthesia due to an occult pheochromocytoma.

Neurofibromatosis is an autosomal dominant disease which varies in terms of severity and can possibly affect all physiological systems. Two types are distinguished according to phenotypical and genetic characteristics: Neurofibromatosis type 1 (NF-1) or von Recklinghausen disease, and Neurofibromatosis type 2 (NF-2). NF-1 is characterized by the formation of neurofibromas primarily in the neuraxis, whereas NF-2 is most commonly associated with bilateral vestibular schwannomas (acoustic neuromas), which are benign tumors in the nerve sheath of the cranial nerve VIII. Concerning NF-1, diagnosis despite technological advances remains mainly clinical according to specific criteria.[2]

It is important to bear into consideration the broad spectrum of clinical manifestations that this particular disease entails.

Hypertrophic cardiomyopathy, heart defects and superior vena cava obstruction due to tumor formation have been observed in NF-1 patients.[1,2] Hypertension on patients with NF-1 may sometimes be secondary due to a latent pheochromocytoma. A cohort study, performed by Mayo Clinic on patients with NF-1 and pheochromocytoma, results in the suggestion that biochemical detection testing for pheochromocytoma is needed prior to elective surgical procedures, and during preconception planning or early pregnancy for women. The presence of a pheochromocytoma requires the exclusion also of syndromes such as MEN-2b, Von Hippel-Lindau, and paragangliomas.[2] The high suspicion of our leading anesthetist for a concomitant pheochromocytoma due to our patient's medical history of neurofibromatosis, and the postponement of the surgical procedure, were of crucial importance.

Although some patients with pheochromocytoma may not experience any symptoms[3] despite increased catecholamine levels, a catecholamine crisis may occur intraoperatively, even spontaneously, due to different mechanisms: mechanical stress due to tumor palpation, psychological stress, or induction in relation to certain drug administration or laryngoscopy.[3,4] Our patient entered the operating room with mild tachycardia and hypertension which was attributed to anxiety, therefore midazolam and fentanyl were administered immediately upon arrival, though without any effect on blood pressure or heart rate. Despite the induction of anesthesia, blood pressure and heart rate remained high and increased after bag-mask ventilation. No attempt to palpate or move the patient was made before or during induction.

Agents used for induction can explain the immediate occurrence of hypertension after drug administration even before any attempt to intubate. Fentanyl, through an increased catecholamine release, and rocuronium, through an adrenergic activation, an atropine-like effect, and increased norepinephrine release from sympathetic nerve endings can trigger a hypertensive crisis.[3,4] Other case reports[5] also associated the same drug combination with an acute catecholamine crisis during induction in patients presenting at the operation room with an undiagnosed pheochromocytoma.

Etomidate was used to avoid any cardiovascular instability during induction.

Bag- mask ventilation coincided with the administration of rocuronium, but it would seem unlikely to trigger hypertension since no Guedel airway was used. Stimulation from removing the laryngeal mask resulted in an increase in blood pressure, which nevertheless responded to the infusion of nitroglycerin.

Regarding other clinical manifestations, 5% of patients with NF-1 present with disease (neurinomas) in the oral cavity and the larynx which may hinder conventional orotracheal intubation. Multiple cervical neurofibromas are associated with painless dislocation of cervical vertebrae, fact that suggests the preoperative radiographic examination of the neck in order to avoid potential damage to the spinal cord during the intubation process. Lung fibrosis, along with vertebral anomalies (kyphosis, scoliosis) potentially hinder normal pulmonary function. Neurofibromas in the gastrointestinal tract present with the risk of perforation, hemorrhage, or concomitant carcinoid syndrome and in the genitourinary system with obstructive ureteral stenosis.[1,2] Cognitive disorders along with increased incidence of epilepsy are observed.

In our case, the patient showed no signs of dyspnea and dysphagia, her vital signs and ECG pre-operatively were normal, she never suffered from lung disease nor has she mentioned any episodes of spasms. She was under close surveillance for her disease and presented no malformations of the spine. She had undertaken general anesthesia for several procedures in the past without mentioning any adverse effects. During preoperative cardiac evaluation, no hemodynamic instability or any abnormal findings were noted. Thus, taking into consideration the gynecologist's persistence to proceed with the operation, on a semi- elective basis, we inquired no further investigations.

We conclude that knowledge of the vast range of NF-1 signs, and symptoms shall guide the questions formed and the examinations demanded by those performing preoperative examination on such patients.

We suggest thorough investigation of NF-1 patients prior to elective surgery due to the diversity of the disease's clinical manifestations. Careful history of the patient's signs and symptoms will guide the clinician's differential diagnosis and will help him/her guide the further systematic radiologic and laboratory examination. Close cooperation between the surgeon, the anesthesiologist, and the cardiologist is required especially for patients with undiagnosed hypertension. It is of great importance that the anesthesiologist handling such cases is aware of how NF-1 affects different physiological systems while adjusting his/her knowledge to the individuality of each patient.

Conflict of interest

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