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Case Report

A Case of Pheochromocytoma Revealed by an Etonogestrel Contraceptive Implant Use

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Abstract: Background: Pheochromocytoma (PH) is a rare tumor developed at the expense of the adrenal medulla and secreting catecholamines. It is also a rare cause of curable hypertension in adults. Case information: We reported a case of PH in a 39-year-old Malagasy woman, with no particular history. The clinic was dominated by the onset of paroxysmal hypertension associated with headache, palpitations, and sweating. Its clinical manifestations were revealed by the insertion of an etonogestrel contraceptive implant. Despite the removal of the contraceptive implant and the taking of an antihypertensive drug based on a calcium channel blocker, the hypertension persisted with a paroxysmal character and always associated with the Menard triad. Results: The diagnosis was made against the elevation of urinary metanephrines and normetanephrines and the presence of a heterogeneous left adrenal mass on computed tomography. Surgical resection of the tumor made it possible to perform an immunohistochemical examination confirming the diagnosis. Without surgical complications, the patient's blood pressure as well as urinary metanephrine and normetanephrine, normalized without taking any antihypertensive drug. Conclusion: Hormonal contraception could be wrongly blamed the cause of hypertension. Then she would just be a triggering factor. Thus, any atypical hypertension following the use of a hormonal contraceptive must encourage the search for a secondary cause such as PH.

Keywords: Contraceptive Implant, Metanephrines, Normetanephrine, Pheochromocytoma

1. Introduction

Pheochromocytoma (PH) is a rare endocrine tumor, developed at the expense of chromaffin cells of the adrenal medulla and producing catecholamine [1]. It is a rare cause of curable hypertension with a prevalence associated with paraganglioma, of the order of 0.2% to 0.6% [2]. PH is probably underdiagnosed because it represents 3% to 7% of incidentally discovered adrenal tumor [3, 4]. However, in the absence of adequate management, cardiovascular morbidity and mortality remain high in PH [5, 6]. In Africa as in Madagascar, very few studies have devoted themselves to this subject. Thus we report a case of PH revealed by an etonogestrel contraceptive implant use, seen in the endocrinology department of the University Hospital Center Joseph Raseta Befelatanana, Antananarivo.

2. Case Presentation

It was a 39-year-old Malagasy woman, who had two pregnancies with two living children and no other specific history. His illness began in 2016 with the discovery of hypertension at 180/100 mmHg, without accompanying signs, following a strong emotion. She was treated by Amlodipine 10 mg daily. After 2 weeks, blood pressure normalized (111/72 mmHg), prompting him to stop his treatment at his own discretion. Since the insertion of an etonogestrel contraceptive implant in 2018, paroxysmal hypertension at 180/110 mmHg reappeared, this time

accompanied by headache, palpitations, and profuse sweating. Despite the resumption of its previous treatment and the withdrawal of the contraceptive implant, the hypertension in paroxysm persisted. She had thus consulted in our department, in 2019. At physical examination, blood pressure was 153/94 mmHg, pulse was 113 beats/min, body mass index was 18.8 kg/m^2. The rest was unremarkable.

Standard biological examinations (kidney function, hemogram, ionograms, lipid profile and fasting plasma glucose) were normal. Urinary normetanephrine and metanephrine were raised to 10.69 µmol/24h (reference range: 0.40-2.10) and 4.49 µmol/24h (reference range: 0.20-1.00), respectively. After having complied with the conditions of sampling, the other hormonal assessments (aldosterone-renin ratio and 24-h urinary free cortisol) showed no abnormality.

Abdominal-pelvic computed tomography (CT) had objectified a heterogeneous mass (size: 4.67 x 4.23 x 3.75 cm) at the expense of the left adrenal with relative Wash-out calculation 15% (Figure 1).

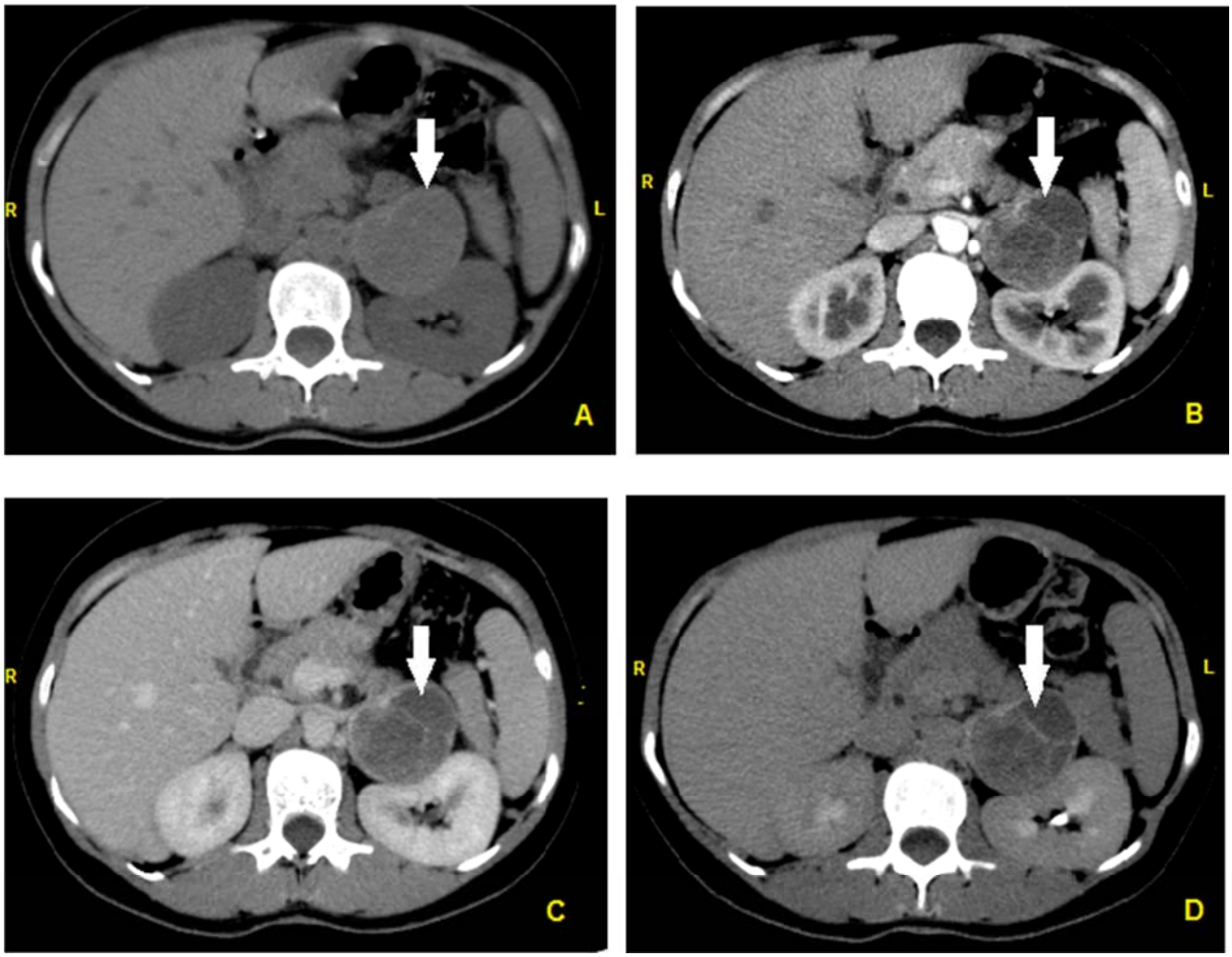

Figure 1. *Abdominal-pelvic computed tomography showing a heterogeneous mass at the expense of the left adrenal gland including the calculation of the relative wash-out (15%) in favor of a pheochromocytoma (In the axial plane, A: non-enhanced CT; B: contrast-enhanced CT arterial phase; C: contrast-enhanced CT venous phase and D: contrast-enhanced CT delayed phase 10 min after).*

The patient underwent a partial left adrenalectomy potting the mass, without any immediate complications. The microscopic anatomopathological examination of the mass revealed, within the adrenal parenchyma, a tumor proliferation made of large or even giant pleomorphic cells, often nucleated, with finely granular cytoplasm, with moderate cytonuclear atypies, of diffuse architecture, by places in spans or nests, richly vascularized and limited at the periphery by fibrous condensation. On immunohistochemical examination, tumor proliferation strongly expresses chromogranin and synaptophysin, compatible with a PH.

Clinical course was favorable with normalization of blood pressure after 3 weeks without drug treatment. Urinary normetanephrine and metanephrine also normalized 12 months after adrenalectomy (Figure 2).

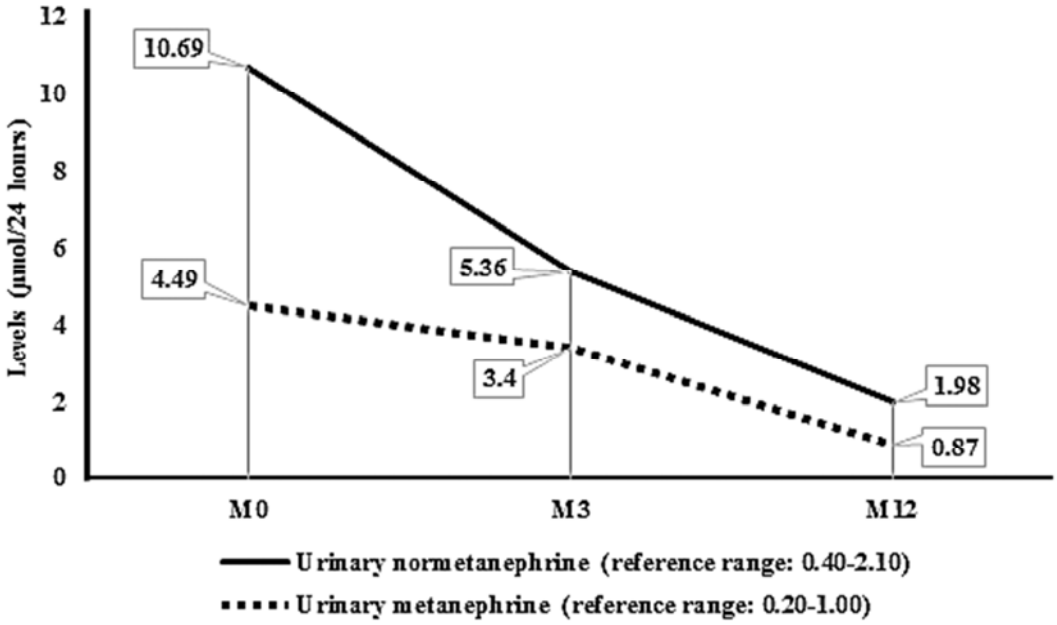

Figure 2. *Kinetics of urinary normetanephrine and metanephrine. M0: before surgery; M3: 3 months after surgery; M12: 12 months after surgery.*

3. Discussion

The clinical presentation of PH is very heterogeneous. It is dominated by the classic triad (headache, palpitations and sweating) associated with paroxysmal hypertension in 50% of cases or permanent in 40% of cases. Normal blood pressure is seen only in 5 to 15% of cases. The presence of this triad has a sensitivity of 89% and specificity of 67%, and of hypertension of 91% and 94%, respectively [7, 8]. Patients can also present other symptoms (orthostatic hypotension, visual disturbances, pallor, weight loss, polyuria, polydipsia, anxiety, tremor, abdominal or chest pain, nausea, vomiting, diarrhea or constipation, chart of heart failure) [9, 10].

In our case, the patient presented with paroxysmal hypertension associated with the classic triad, revealed by an etonogestrel contraceptive implant use. Indeed, a high concentration of exogenous estrogens cause rapid release of dopamine, via the cyclic adenosine monophosphate/Protein kinase A pathway and N-type calcium channels, in PH cells [11, 12]. In addition, the estrogen of hormonal contraceptives activates the Renin-Angiotensin-Aldosterone System, causing a significant increase in blood pressure. Hypertension affected 2.8% of women on this contraceptive with an increase of 8 and 6 mmHg for systolic and diastolic pressure, respectively [13, 14].

The dosages of catecholamine metabolites (metanephrines, normetanephrines) in plasma or urine for 24 hours allow the diagnosis of PH to be made. This urine assay that we used for our patient already has excellent sensitivity (97%) and specificity (91%) [15]. Furthermore, the combination of methanephrine and dopamine metabolite 3-methoxytyramine plasma assays offers slightly more sensitivity (99%) [2].

For the topographic diagnosis, abdominal-pelvic CT non- and contrast-enhanced is the most commonly used imaging test. It allows visualizing tumors larger than 0.5-1 cm and has the advantage of a low cost. Its sensitivity is high, estimated to be greater than 95% [16, 17]. Magnetic resonance imaging is only to be asked in some situations (children, pregnant women, proven allergy to CT contrast). Functional imaging such as ^{123}I-metaiodobenzylguanidine (MIBG) scintigraphy and positron emission tomography coupled with CT scanning (PET/CT), makes it possible to locate a tumor not seen in previous imaging and to search for multi-focal or metastatic disease [2, 18].

Once the diagnosis of PH is made, the cornerstone of treatment remains surgical resection. It must be preceded by medical treatment based on the combination of alpha- and beta-blockers in order to control blood pressure before and after surgery. The use of calcium channel blockers has also been proven in the literature [3].

After adrenalectomy, the rate of recurrence of PH varied between 6 to 23%. And the size of a tumor greater than 5 cm was identified as a predictor of this recurrence [19, 20]. Consequently, patients must benefit from clinical (adrenergic signs, blood pressure) and biochemical (metanephrines, normetanephrines) follow-up once a year in the case of unilateral PH less than 5 cm in diameter, and at 6 months then annually in the event of PH more than 5 cm in diameter, family history of PH or paraganglioma [18, 21]. In the event of a further elevation of these biochemical markers, metastases should be sought by MIBG scintigraphy and the PET/CT [22].

4. Conclusion

Pheochromocytoma is a rare cause of curable hypertension that can be mistaken for the side effect of a hormonal contraceptive, like an etonogestrel contraceptive implant. The paroxysmal character of hypertension associated with the

classic triad must evoke its diagnosis. Biochemical and radiological explorations allow the diagnosis of the tumor to be made. The main treatment consists of surgical resection followed by clinical and biological follow-up. Therefore, any atypical hypertension following a hormonal contraceptive use must be the subject of research for a secondary cause such as pheochromocytoma.

Statement of Ethics

The patient has given his informed consent.

Competing Interests

The authors declare that they have no competing interests.

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