Management of pheochromocytoma during pregnancy from diagnosis to laparoscopic adrenalectomy.

A case report and review of literature

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INTRODUCTION: *Pheochromocytoma is an endocrine tumour of chromaffin cells. It can be diagnosed either sporadically or in the context of hereditary syndromes (e.g. Von Hippel Lindau, Neurofibromatosis type 1 and multiple neuroendocrine neoplasia type 2). During pregnancy, its frequency is very low (about 0,007%). This tumour causes paroxysmal hypertension in 0,1-0,6% pregnant women, because of an overproduction of catecholamines. If undiagnosed and non-treated, it's associated with high maternal and fetal mortality (40-50%). We report the case of a 30-year-old female diagnosed with pheochromocytoma during pregnancy at week 31 of gestation. In a multidisciplinary team made of surgeons, gynaecologists, anaesthetists, geneticists and endocrinologists we evaluated the case and according to literature, we choose a surgical approach after childbirth: performing a laparoscopic right adrenalectomy.*
DISCUSSION: *In pregnancy, pheochromocytoma is a rare clinical condition. Gold standard treatment is laparoscopic adrenalectomy. However, the optimum timing of surgery is a challenge.*
CONCLUSION: *Timely diagnosis of pheochromocytoma in pregnant women with hypertension and appropriate therapeutic management can lead to improve maternal, fetal and neonatal outcomes. The multidisciplinary team is necessary to recognize the symptoms and to adopt the right pre – and post – operative treatment. Laparoscopic adrenalectomy after delivery is safe and feasible even though the surgical procedure should be performed by an experienced surgeon.*

KEY WORDS: Pheochromocytoma, Pregnancy, Laparoscopic adrenalectomy and pregnancy, Management of pheochromocytoma, Laparoscopic adrenalectomy, Adrenalectomy, Pregnancy and pheochromocytoma

Introduction

Pheochromocytoma (PCC) is a rare catecholamine-producing tumour of chromaffin cells whose incidence, during pregnancy, is 0,007% [1,2]. The main symptoms are paroxysmal hypertension, paroxysmal tachycardia, diaphoresis, palpitations, headache, excessive sweating, tremor or anxiety [3]. Symptoms of PCC often worsen during pregnancy, due to both the increased blood supply to the tumour and enhanced catecholamine secretion. An undiagnosed PCC is associated with very high maternal and fetal mortality, estimated at 40-50% [1,2,4]. Pheochromocytoma in pregnant patient is diagnosed by measuring elevated levels of metanephrines (catecholamine metabolites) in blood or 24 hours urine, ultrasound or magnetic resonance image (MRI) (the preferred technique for localizing pheochromocytomas) performed without gadolinium-based contrast agents [7].

Pharmacological treatment before surgical procedure consists of an alpha-blockade for the control of hypertension and to preserve adequate uteroplacental circulation [4-7]. Laparoscopic adrenalectomy (LA) is the gold standard surgical procedure; if it's diagnosed within 24

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weeks of pregnancy, LA can be performed in the second trimester, while if its's diagnosed in the third trimester, it can be postponed after delivery with appropriate medical pre-treatment [5].

Case Presentation

A 30-year-old primipara at 31 weeks of gestation referred to Department of Gynaecology for hypertension (blood pressure 220/100 mmHg), headache and severe right-sided abdominal pain. The patient was naive to surgery but was affected by chronic hepatitis B infection undergoing antiviral treatment with virologic suppression. In addition, her clinical history was negative for both essential and secondary hypertension (Cushing syndrome, chronic kidney injury, PCC or hyperaldosteronism).
Initially, she was unsuccessfully treated with nifedipine 40mg/day and alpha-methyldopa 2mg/day. Laboratory tests showed an increase 24-hours urinary levels of catecholamines and their metabolites (noradrenaline levels were 1017 μg/24h range < 97 μg/24h and normetanephrines levels were 3.97 mg/24h range 1.05-3,54 mg/24h) while adrenalin and dopamine levels were normal (16,4 μg/24h range <27 μg/24h and 200 μg/24h range <400 μg/24h), parathyroid hormone (PTH) (58 pg/ml), serum calcium (8.8 mg/dl) and serum calcitonin (3,4 pg/mL) were range. Proteinuria was not present. Abdominal ultrasound described an adrenal mass of 4 cm x 5 cm. RMN without gadolinium showed the presence of 48x38x47 mm expansive formation in the right adrenal loggia, hypointense in T1 and hyperintense in T2 (Fig. 1).
Subsequently the gynaecologist submitted the case for multidisciplinary evaluation (endocrinologist, geneticists, anaesthesiology and surgeon) that opted for a right adrenalectomy after planned caesarean section.
After genetic counselling, we analyzed these susceptibly genes: VHL, RET, SDHA, SDHB, SDHC, SDHD, SDHAF2, NF1, TMEM127, MAX, EGLN1/PHD2, EGLN2/PHD1, KIF1β, IDH1, HIF2α, FH and ATRX. We did not encounter any DNA mutations. As for blood pressure management, the patient was treated with doxazosin, initially 1mg/die up to 4 mg/die, and with an appropriate hydration (500ml/die of physiologic saline solution). We experienced an excellent blood pressure control until surgery.
To preserve fetal lung maturation, a corticosteroid-based prophylaxis with betamethasone was administered during the 33rd gestational week, without any increase in maternal blood pressure values. At 36th gestational week, an urgent Caesarean section was performed under general anaesthesia because cardiotocography showed signs of fetal distress. No complication was referred during the surgical procedure. The new-born was a female of 3,250 kg with an APGAR score of 6 and 7 at the first and at the fifth minute after birth. She was discharged from the hospital after 6 days without complications.
One month after the caesarean section, the patient was referred to our Department to perform the laparoscopic right adrenalectomy (LRA). The day before surgery, she received 1500ml of physiologic saline solution for prevent a sudden episode of hypotension after removal of the tumor. The surgical approach was laparoscopic transperitoneal right adrenalectomy: the patient was placed in a modified flank position, 45 degrees back from vertical, three ports were used in triangulation in subcostal position and an additional fourth port for the liver retraction on subxiphoid site were positioned. During surgical procedure we found difficulties related to the position of the gland (right adrenal gland): proximity to the inferior vena cava and moderate adhesions to the hepatic margin and to right kidney. During adrenal gland manipulation and adrenal vein dissection, the

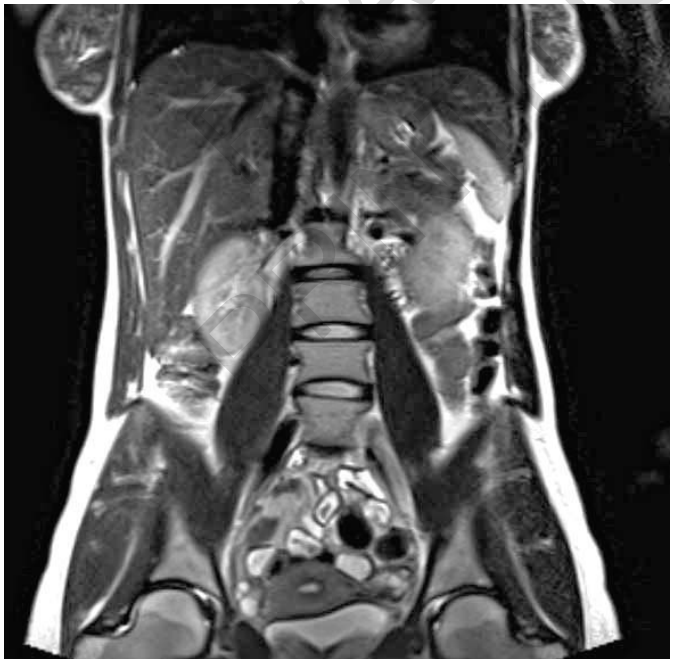

Fig. 1. Abdominal pre-operative MRI.

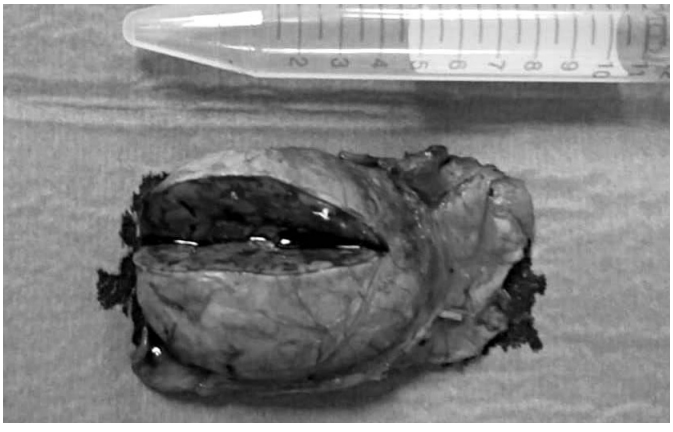

Fig. 2. Photograph of the tumor.

anesthesiologist, according with surgeon, administered sodium nitroprusside infusion (0.8 μg/kg/min for approximately 7 min.) and intermittent boluses of esmolol 10 mg IV (total 20 mg) to maintain blood pressure. At the end of surgery, 1 gr hydrocortisone bolus was administered. Intraoperative blood loss was 100 cc. The blood pressure was normal in the post-operative day. The patient was discharged on the third post-operative day without complications.

The histological examination detected a PCC made of neoplastic cells containing granules of norepinephrine and epinephrine without definite lymph vascular invasion. Immunohistochemistry showed chromogranin A-positive granules (Fig. 2).

One year later, the follow-up MRI showed the absence of any other abdominal masses. At both six-month and one-year follow-up, blood pressure values were normal.

Discussion

In pregnancy, PCC is a rare clinical condition and it could be often misdiagnosed either with preeclampsia or eclampsia [1, 8-10]. Pre-eclampsia occurs after 20 weeks of pregnancy and/or within 24-48/hours after delivery [11]. Pre-eclampsia, additionally to hypertension, is characterized by proteinuria (higher than 300/mg in 24/h); eclampsia has also seizures [11]. PCC symptoms can occur at any time during pregnancy and are caused by catecholamines overproduction, local mass effect or metastasis. Its symptoms are hypertension, headache, sweating, tachycardia, diaphoresis and palpitations [12]. However, other fewer common symptoms are reported: pallor, dizziness, dyspnea, polyuria, seizures, nuchal pain, nausea, vomiting and abdominal pain [2,13]. PCC in pregnancy in 20-40% of cases is associated with genetic syndromes [5,6]. In 2% of the patients with PCC, there is an association with neurofibromatosis, and they have *café-au-lait* spots, freckles and fibromas [2,4]. Long-standing hypertension may damage heart, kidney, eyes, central nervous system and deregulate glucose metabolism [12]. In pregnant patients with PCC, hypertension is the most common symptom, occurred in 87% of cases (being paroxysmal, unlike eclampsia and preeclampsia) [14,15,17]. Other symptoms are postural hypotension (reported in 50%), hyperglycaemia and cardiomyopathy [18,19]. In our case, the patient presented hypertension (blood pressure 220/100 mmHg), headache and severe right-sided abdominal pain. During pregnancy, catecholamines overproduction induces vasoconstriction of uteroplacental arterial circulation, uteroplacental insufficiency, which can lead to spontaneous abortion, fetal growth restriction (FGR), hypoxia and intrauterine fetal death. During the last decade, an early diagnosis and an appropriate treatment reduced maternal and fetal deaths (respectively <5% and <15%) [1-4]. During the last decade, an early diagnosis and an appropriate treatment reduced maternal and fetal deaths (respectively <5% and <15%) [1-4]. PCC in pregnancy in 20-40% of cases is associated with genetic syndromes [5,6]. A recent review showed a reduction of the incidence fetal loss rate in the past 50 years by about 45% [1,20] because of the early diagnosis and early pharmacological and surgical treatment [1,2,17].

To properly diagnose PCC, biochemical tests and diagnostic imaging are required. Biochemical tests evaluate catecholamine (normetanephrine and adrenaline) and their metabolites (normetanephrine and metanephrine) in the plasma and urine. During healthy pregnancy and in patients with preeclampsia, catecholamine metabolism is unaltered. However, plasma and/or 24-h urine concentrations of (nor)metanephrine are required for pregnant with suspect of PCC [21]. In our case, the concentrations of noradrenaline and normetanephrine in the 24-h urine were elevated, while adrenalin, dopamine and uric acid in range. Proteinuria was absent. MRI is the gold standard imaging technique in pregnant patients. In our patient, abdominal ultrasound described an adrenal mass of 4x5 cm and MRI confirmed the presence of 48x38x47 mm expansive formation of right adrenal gland.

Given the possibility of association with hereditary syndromes (20-40% of patients with PCC), genetic counselling should be considered [1,23]. We analyzed these susceptible genes: VHL, RET, SDHA, SDHB, SDHC, SDHD, SDHAF2, NF1, TMEM127, MAX, EGLN1/PHD2, EGLN2/PHD1, KIF1β, IDH1, HIF2α, FH and ATRX) [23]. The geneticists excluded DNA mutations.

A multidisciplinary team made of gynaecologists, geneticists, endocrinologists, endocrine-surgeons and anaesthesiologists should take control over PCC management during pregnancy the optimal medical therapy is still controversial [1,20,24]. Initially, we treated the hypertension and prevented the paroxysms with alpha blockers like doxazosin [25]. Phenoxybenzamine have high incidence of reflex tachycardia and, in a study on neonatal effects after long-term exposition, it seems to be associated with hypotension and respiratory depression [26]. Doxazosin is associated with a good neonatal outcome and neonatal hypotension and respiratory depression are not mentioned [27]. Beta-adrenergic receptor blockers can be added in case of catecholamine-induced tachycardia and arrhythmia and alpha-blocker-induced reflex tachycardia [25]. The most common beta-blockers used during pregnancy are propranolol and atenolol. If the hypertension is not stabilized, it's useful to add a calcium channel blockers (CCBs) [16]. Our patient has been treated and hydrated with doxazosin 4mg/die and 500ml/die. The use of doxazosin did not determine adverse effect on the foetus.

Gold standard treatment of PCC is LA. The optimum timing of surgery is a challenge. We consider gestational age, maternal and fetal response to α-adrenergic receptors blockade and bilateral tumor [1,4,5]. We searched on

PubMed adrenalectomy during pregnancy from 1998 and 2019 using the following keywords: "pheochromocytoma and pregnancy", "adrenalectomy and pregnancy". In literature data, when PCC is diagnosed within the first 24 weeks of pregnancy with adequate alpha-blockade, adrenalectomy can be performed during the second trimester [1,15-17]. The diagnosis during the third trimester requires a postposed surgical procedure after the delivery [1,28]. The delivery can be performed with concurrent or delayed LA [1,28]. In this way we found 33 cases of adrenalectomy for PCC during pregnancy. In particular, 3 patients were treated beyond the 24th week, 1 in the first trimester, 3 during caesarean section and 12 after delivery (PCC was diagnosed during pregnancy) and 14 in the second trimester (of them 1 with twin pregnancies and 1 with bilateral PCC) [1,5-8,15-18]. Then, 20 patients were treated with LRA, 9 with laparoscopic left adrenalectomy (LLA), 1 with laparoscopic bilateral adrenalectomy and 3 with open right adrenalectomy (2 of these during caesarean section) [1,5-8,15-18].

A paper reported three cases of bilateral adrenal PCC [16]. In these cases, a unilateral adrenalectomy was performed for the largest lesion; we excluded from our review 2 cases secondary to hereditary syndrome [16]. In all paper analyzed, no case of maternal mortality is reported, while 2 cases of infant mortality are described, 1 in a patient treated with Caesarean section (CS) and LLA at 28 week of pregnancy and 1 case of emergency CS at 28w with baby died several days after birth and open left adrenalectomy plus Hartmann's resection at 29w [16]. Also, there are two cases of abortion in patients treated with LA at 12 and 14 weeks of pregnancy [8,9,15]. From literature data, surgery should be avoided both in the first trimester, because of incomplete organogenesis and abortion is highly likely, and in the third trimester because the enlargement of uterus precludes adequate access and evaluation of the abdomen [8,9]. There is a consensus towards to consider the second trimester as the ideal time surgery [5,15,16,24]. According to literature data, we performed LA one month after the delivery. To control the blood pressure, our patient was administered with doxazosin 4 mg/die until surgery.

Conclusion

Timely diagnosis of PCC in pregnant women with hypertension and appropriate therapeutic management can lead to improve maternal, fetal and neonatal outcomes. The multidisciplinary team is necessary to recognize the symptoms and to adopt the right pre – and post – operative treatment. In our case, the collaboration between anaesthesiologist, gynaecologist endocrinologist and surgeons, allowed the best treatment for the patient from diagnosis to surgery. Laparoscopic adrenalectomy after delivery is safe and feasible even though the surgical procedure should be performed by an experienced surgeon.

Riassunto

Il feocromocitoma è un tumore endocrino delle cellule cromaffini. Questo tumore può essere riscontrato in forma sporadica o nel contesto di sindromi ereditarie (ad esempio Von Hippel Lindau, Neurofibromatosi di tipo 1 e neoplasia neuroendocrina multipla di tipo 2). Durante la gravidanza, la sua frequenza è molto bassa (circa 0,007%). L'ipertensione parossistica è conseguente ad una iperproduzione di catecolamine e interessa lo 0,1-0,6% delle donne gravide. Questo tumore è associato a un'elevata mortalità materna e fetale (40-50%), per questo è essenziale una diagnosi precoce.

In questo lavoro descriviamo il caso di una donna di 30 anni affetta da feocromocitoma diagnosticato alla 31ª settimana di gestazione. La gestione della paziente è stata affrontata da un team multidisciplinare composto da chirurghi, ginecologi, anestesisti, genetisti ed endocrinologi. Abbiamo scelto di attuare un approccio conservativo durante la gravidanza per poi asportare il tumore chirurgicamente, un mese dopo il parto, eseguendo una surrenectomia destra laparoscopica.

Il trattamento gold standard è chirurgico, tuttavia, non vi è un consenso unanime sul giusto timing.

La diagnosi tempestiva e un'adeguata gestione terapeutica del feocromocitoma nelle donne in gravidanza con ipertensione può ridurre la mortalità materna, fetale e neonatale. Il team multidisciplinare è necessario sia per ottenere una diagnosi tempestiva che per adottare il giusto trattamento pre – e post – operatorio.

Nel nostro caso, questa gestione collegiale ha consentito di intraprendere le migliori scelte terapeutiche per la paziente. A nostro giudizio, la surrenectomia laparoscopica dopo il parto è una procedura sicura e fattibile purché sia eseguita da un chirurgo esperto.

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Commento e Commentary

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La diagnosi precoce ed il corretto management terapeutico del feocromocitoma in gravidanza sono fondamentali per una prognosi materna e fetale favorevole.
La diagnosi è purtroppo complessa. In un'alta percentuale dei casi il sospetto origina in seguito al riscontro di ipertensione arteriosa parossistica e di nuova insorgenza. Il dosaggio sierico ed urinario dei metaboliti delle catecolammine e le tecniche di immagine confermano la diagnosi.
L'ipertensione in gravidanza è tuttavia comune, quindi la presenza di un tumore delle ghiandole surrenali va considerata in caso di ipertensione severa o fluttuante, ipertensione associata a sudorazione eccessiva, cefalea, tachicardia o improvvisa perdita dei sensi in una paziente ostetrica.
In letteratura pochi sono i casi documentati di feocromocitoma diagnosticato nel corso di una gravidanza e nessun articolo suggerisce quale sia il timing corretto per la gestione ottimale della paziente e per il miglior outcome fetale.
Il caso presentato è interessante perché pone particolare attenzione alla terapia farmacologica antiipertensiva volta al raggiungimento di un'epoca gestazionale adeguata per l'espletamento del parto e sottolinea l'importanza della scelta del timing per un giusto compromesso tra prematurità fetale e morbilità materna.

* * *

Early diagnosis and correct therapeutic management of pheochromocytoma in pregnancy are essential for a favorable maternal and fetal prognosis.
The diagnosis is unfortunately complex. In a high percentage of cases, the suspicion arises following the finding of paroxysmal and new onset arterial hypertension. Serum and urinary assay of catecholamine metabolites and imaging techniques confirm the diagnosis.
However, hypertension in pregnancy is common, so the presence of a tumor of the adrenal glands should be considered in the case of severe or fluctuating hypertension, hypertension associated with excessive sweating, headache, tachycardia or sudden loss of consciousness in an obstetric patient.
In the literature, there are few documented cases of pheochromocytoma diagnosed during pregnancy and no article suggests the correct timing for optimal patient management and for the best fetal outcome.
The case report is interesting because it makes you pay particular attention to antihypertensive drug therapy aimed at achieving an adequate gestational period for the completion of childbirth and emphasizes the importance of the choice of timing for the right compromise between fetal prematurity and maternal morbidity.