CASE REPORT

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Paraganglioma: A Difficult and Threatening Ordeal of Pregnancy

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Abstract

Paraganglioma (PGL) in pregnancy is an extremely rare condition, and its diagnosis is often difficult because the clinical symptoms can mimic those of pre-eclampsi a gestational hypertension, and gestational diabetes. Here we report the case of a 24-year-old female primigravida – known case of hypothyroidism who presented with labile hypertension, resting tachycardia and hyperglycaemia with proteinuria at 27-week gestation. We suspected that she might have gestational diabetes along with hypertension and a catecholamine secreting tumour (CST) as her renal Doppler was suggestive of an extra-adrenal mass at left lumbar region which was confirmed on MRI of abdomen and pelvis, and serum catecholamine levels were found to be significantly increased. She underwent laparoscopic mass removal and the pathology confirmed PGL. When typical paroxysmal hypertension and resting tachycardia is accompanied by headache, palpitation, and sweating during the gestational period, an adrenal or extra-adrenal tumour should be suspected.

Key words: Catecholamine secreting tumours (CST), Paraganglioma (PGL), Pheochromocytoma (PCC), plasma free metanephrin and normetanephrin, preeclampsia.

Introduction

Pre-eclampsia/eclampsia is one of the leading causes of maternal mortality. Worldwide 50,000 maternal deaths occur every year, occurring at a rate of 1.5/1,00,000 live births[1,2]. Pre-eclampsia can be confused with many other clinical diseases including acute fatty liver, cholestasis of pregnancy, catecholamine-secreting tumors like PCC and PGL[3].

PCC/PGL is a rare type of CST that arises from chromaffin tissues in the adrenal gland and rarely seen during pregnancy (Approximately 7 in 1,00,000) and PCC is more common than PGL[4,5]. 90% of pregnant women have PCC or PGL symptoms just before delivery, which may lead to a delay in diagnosis and increased health risks for both the foetus and the mother[6(B2)]. PCC/PGL might be suspected in a patient by observing characteristic manifestation that is 5 H's: Paroxysmal hypertension, Headache, Hyperhidrosis, Hyperglycaemia, and Hypermetabolism[7(G0)].

Case history

A 24-year-old primigravida with 27 weeks of gestation was referred in our hospital with recently detected hypertension [Blood pressure (BP) was 210/110 mm of mercury (Hg)] with hyperglycaemia (Random blood sugar was 140 mg/dl) with proteinuria which was initially misdiagnosed as pre-eclampsia and gestational diabetes.

She gave a history of history of headache, sweating, and intermittent palpitations since the last 2 years which was relieved with medication. She had labile blood pressure (details mentioned in Table I). Due to her persistent symptoms and uncontrolled blood pressure, she was investigated for secondary hypertension in form of a renal Doppler. It was suggestive of a large, well-defined, solid heteroechoic predominantly hypo echoic lesion measuring 62 x 66 x 70 mm (AP x TR x CC) in the left lumbar region anterior to the perirenal fascia suggestive of PCC while other investigation suggestive of proteinuria and hyperglycaemia (only single reading of RBS was 140 mg/gl. All other readings were normal with a normal glycosylated haemoglobin).

Table I:

Investigations

24-hours ambulatory blood pressure and pulse rate monitoring reports			
Parameters	**Average value**	**Maximum**	**Minimum**
Systolic blood pressure (mm of Hg)	144	170	123
Diastolic blood pressure (mm of Hg)	103	119	86
Pulse (Beats/minute)	95	118	80

To confirm the diagnosis, her MRI abdomen and pelvis was done without revealing foetus identity, along with plasma free metanephrin and normetanephrin. The MRI report was suggestive of a solid round-to-oval shaped lesion measuring approximately 66 x 68 x 80 mm (AR x TR x CC) with smooth margin noted in retroperitoneum just anterior to the left

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kidney suggestive of neoplastic aetiology (most likely extra-adrenal PGL/PCC Fig. 1, 2, 3) while serum plasma free metanephrin and free normetanephrin values were on the higher side (Table I) so blood parameters and radiological findings were correlated with our diagnosis of PGL.

As the patient was a primigravida, our primary goal was mother and foetus safety with control of blood pressure. Controlling blood pressure was difficult as BP was fluctuating from systolic 210 - 100 mmHg and diastolic was 120 - 80 mmHg. BP was controlled with an alpha-blocker and later on, an addition of a beta-blocker was done. After starting medications, patient was symptomatically better but after 8 days of admission she developed foetal distress in the form of foetoplacetal insufficiency. As the mother's health was deteriorating, termination of pregnancy was planned.

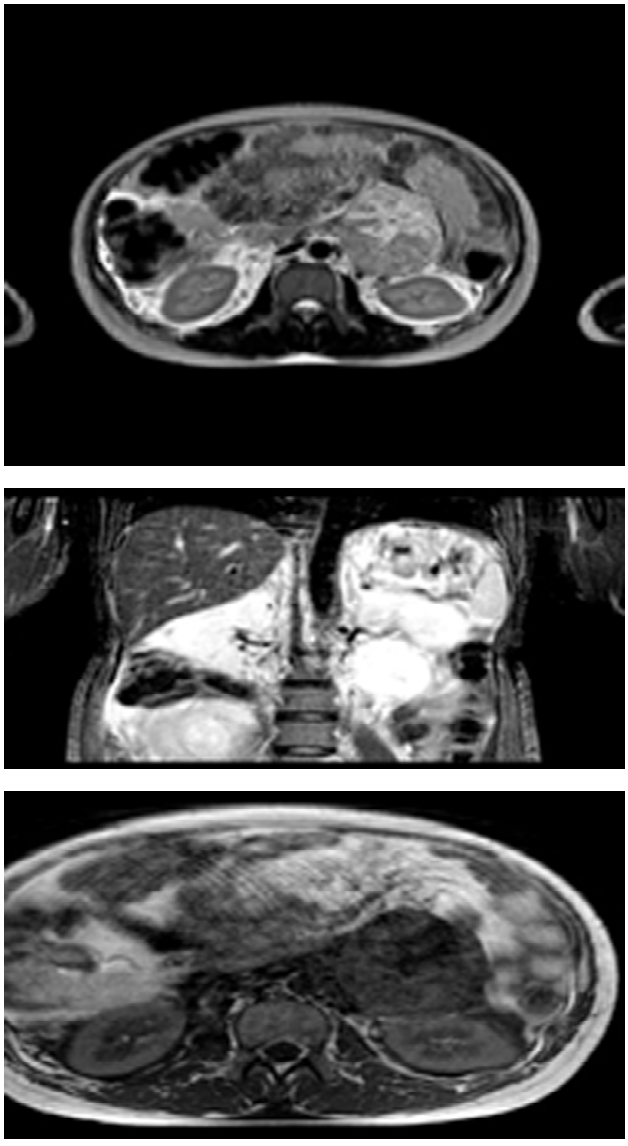


Fig. 1, 2, 3: *MRI abdomen and pelvis.*

We could not revive the foetus which delivered vaginally with the help of magnesium sulphate; but mother's blood pressure was under control with the help of alpha-blocker (Prazosin) and beta-blocker (labetalol) and patient was discharged with medication.

After 1 week of discharge, the patient's reassessment was done. At that time her blood pressure was under control with help of medications, so her DOTA scan was done. It was suggestive of a well-defined mass of 67 x 63 x 80 mm with increased somatostatin receptor expression seen at left lumber region of abdomen (SUV max = 6.6) located at lower pole of left kidney. These findings were suggestive of a neuro-endocrine tumour (NET) – extra adrenal PGL Fig. 4 and 5. After the scan, patient was planned for laparoscopic extra-adrenal mass removal with multidisciplinary approach, mass removed of size 67 x 62 x 27 mm (Fig. 6, 7) and studied histopathologically which was suggestive of PGL(Fig. 8, 9).

It was a multidisciplinary approach; after removal of the mass, the patient was kept in the intensive care unit for 2 days for observation. Post-operatively, patient had one episode of rise in blood pressure (170/100 mm of Hg) along with tachycardia which was we controlled with a beta-blocker and the patient discharged without any medication.

Table II:

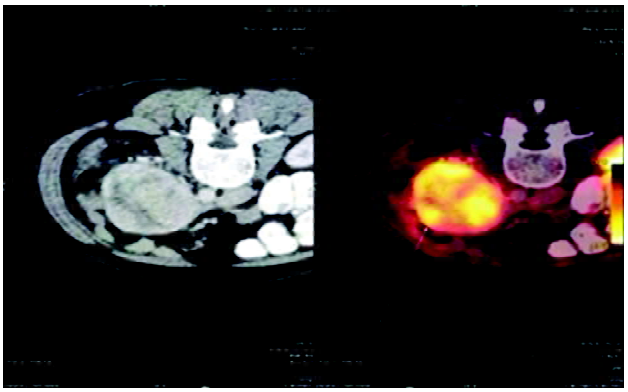
Lab. parameters of the patient

Parameters	Patient values	Normal values
Plasma free metanephrine	380 pg/ml	< 65
Plasma free normetanephrin	7196 pg/ml	< 196
Total proteins	5.7 gm/dl	6.3 - 8.2 gm/dl
TSH	9.8	
Serum cortisol	22.17 ug/ml	
Urine albumin	3+	
24-hour Urinary protein	4839 mg/24 hr	20 - 140

Discussion

According to the 2017 World Health Organisation (WHO) classification, adrenal CST is divided into two categories: intra-adrenal PGL, which is more commonly referred as PCC and extra-adrenal PGL. Because the two tumour types cannot be distinguished based on histological characteristics, anatomical location is utilised to separate them[8,9].

Extra-adrenal PGL can develop from either the sympathetic or parasympathetic paraganglia chain. Generally sympathetic PGL is a catecholamine secreting functional tumour and primarily seen in the abdominal and thorax



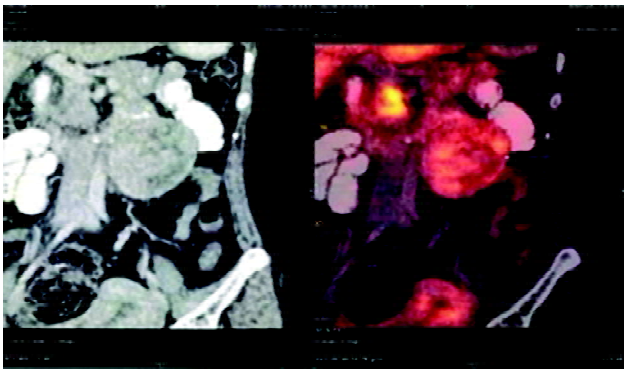


Fig. 4, 5: *Gallium-68 DOTANOC PET SCAN.*

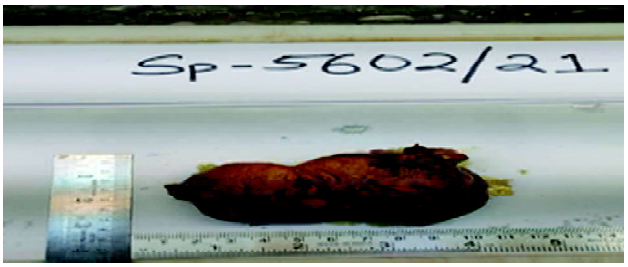
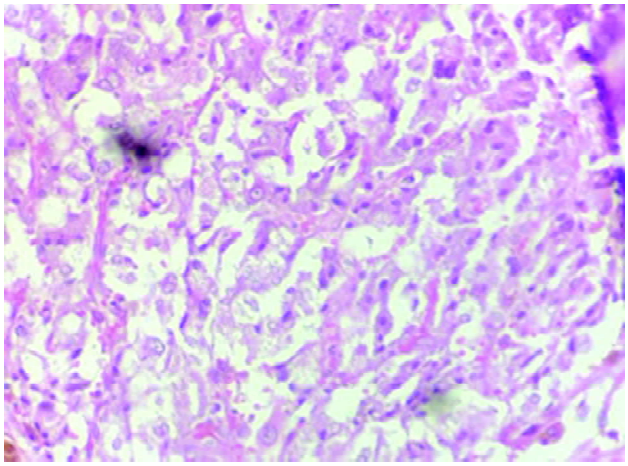


Fig. 6, 7: *Gross picture of Paraganglioma.*

area[10]. While PGL deriving from the parasympathetic chain are catecholamine non-secreting tumours and located in neck and skull base[11]. In this case report we detected PGL in the abdominal area. Many-a-times the diagnosis for CST gets delayed in pregnancy as it is difficult to differentiate signs and symptoms of other common disorders which are



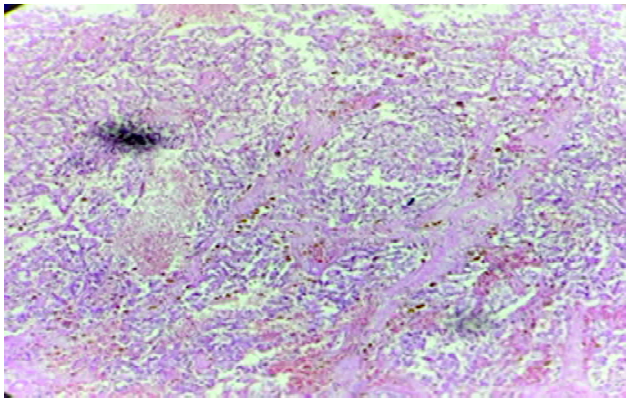


Fig. 8, 9: *Histopathological examination of tumour.*

observed during pregnancy, i.e., hyperemesis gravidarum, gestational induced hypertension, pre-eclampsia, eclampsia, and gestational diabetes mellitus[12,13].

In this case, the patient presented with confusing clinical symptoms and laboratory findings in which PGL mimics pre-eclampsia or gestational hypertension and gestational diabetes. Severe hypertension along with proteinuria go in favour of severe pre-eclampsia, although resting tachycardia and severe sweating are not typical signs of this disease. Generally, pre-eclampsia occurs in the second trimester after 20 weeks of gestation as compared to CSTs which can show symptoms and signs at any phase of gestation[14]. The fact that this patient only had the first paroxysmal episode of hypertension which was labile in nature associated with resting tachycardia in the third trimester, led us to look for PCC/PGL as a differential diagnosis. However, previously asymptomatic tumour can show symptoms for the first time at a late gestational age due to increased abdominal pressure due to foetal movement, uterine enlargement, uterine contraction, labour, physical and emotional stress, although catecholamines do not cross placenta but utero-placental insufficiency occurs due to paroxysmal reduction and

increment of blood pressure that may lead to intrauterine hypoxia[15].

When diagnosis of CSTs is suspected from clinical history and physical examination, immediate biochemical markers should be performed for confirmation of diagnosis. The essential test for diagnosis of CSTs is confirmation of excessive catecholamine secretions[16]. Most sensitive tests for diagnosis of PCC and PGL are measurement of plasma free metanephrin, normetanephrin or urinary fractionated metanephrin; but evidences suggest that plasma free metanephrin and nor metanephrin are better than urinary parameters for diagnosis of pheochromocytoma[17]. MRI without Gadolinium is the diagnostic imaging test of choice in pregnancy in a suspected case of PCC/PGL as it provides good visualisation of abdomen and pelvis without radiation[18], but a golden test for diagnosis of PCC/PGL is MIBG (Metaidobenzylguanidine) scan but not recommended in pregnancy due to its potential undesirable effect on foetus[19].

Compared to recent nucleotide (DOTA PET, FDOPA PET and FDG PET) scans, MIBG and MRI scan are less sensitive[20-22]. Among nucleotide scan, DOTA PET SCAN is more sensitive compared to others[23].

The management of CST in pregnancy involves blood pressure control and avoidance of labile blood pressure and it requires proper equilibrium between vasodilatation and vasoconstriction to avoid foetal demise. Although surgical removal of tumour is the definitive treatment, medical management also important[24].

Phenoxybenzamine, a non-specific, long-lasting alpha-adrenergic antagonist is the drug of choice even though it crosses the placenta. Fair neonatal outcomes after phenoxybenzamine treatment in pregnancy have been reported[25,26]. Neonatal respiratory distress and hypotension have been documented in some cases whose mothers were treated with phenoxybenzamine. It is therefore suggested that neonates should be monitored after delivery whose mothers were taking pheoxybenzamine for treatment[27]. Maternal tachycardia observed during use of phenoxybenzamine is due to noradrenaline release from presynaptic nerve. While hypotension documented due to its prolonged half-life and irreversible blockade of alpha-adrenoceptors[25]. Alternatives to phenoxybenzamine include other alpha-adrenergic antagonists such as prazosin, and doxazosin. These agents produce less tachycardia with shorter duration of action when compared with phenoxybenzamine, which allow them in dose titration and decreased evidence of post-operative hypotension[15,28]. In our case, the patient's blood pressure was under control on alpha-blockers and beta-blockers before surgery and all antihypertensive drugs were stopped after surgery. Methyldopa which is commonly used for hypertension during pregnancy may worsen the symptoms of CST; hence this drug should be avoided[29].

Traditionally, it has been suggested that vaginal delivery should be avoided in pregnant women with PGL/PCC[30], as there is a high-risk of hypertensive crisis during active labour but some cases are noted in literature of successful vaginal delivery without maternal and foetal mortality[31-35]. Unfortunately, in our case, foetus could not survive which was delivered by vaginally without damaging mother's health, as magnesium sulphate inhibits secretions of catecholamine.

In cases where the CST diagnosis is established during the third trimester, the laparoscopic approach may be difficult due to the enlarged uterus. Therefore, medical treatment is commenced with observation until sufficient foetal maturity is achieved. Delivery is then planned during final trimester, with concurrent or delayed adrenalectomy[5,14]. In our case, the mass was removed via laparoscopic approach after 1 week of delivery. After surgical removal of CST, careful post-surgical vital monitoring is required as the patient may land into hypovolumic shock due to sudden fall in catecholamine levels after removal of CST[36]. But in our case it was managed properly and the patient was discharged without any medication for hypertension.

Conclusion

Although PGL is a rare cause of hypertension in pregnancy, it should be considered in the differential diagnosis in the pregnant female who presents with atypical hypertension and symptoms. A multidisciplinary team approach is important for the management of pregnancy and PGL for better outcome of patient.

Renal Doppler

Grade II medical renal disease with large well defined solid hypo echoic lesion measuring 6.2 x 6.6 x 6.1(APXTRXCC) in left lumbar region anterior to perirenal fascia suggestive of neoplastic aetiology likely extra adrenal PCC.

Section study shows a well circumscribed tumour arranged in lobular and zellballen pattern separated by fibrous septa. Individual tumour cells are round to polygonal with abundant granular cytoplasm, round to oval nucleus with stippled chromatin. Mitoses (approximately 10/10 Hpf) noted. Spindle shaped sustentacular cells with slender nuclei are also seen. There is no capsular/vascular invasion. Area of haemorrhage and congested blood vessels noted.

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