Original Research Paper

Volume - 14 | Issue - 06 | June - 2024 | PRINT ISSN No. 2249 - 555X | DOI : 10.36106/ijar

Obstetrics & Gynaecology

A LESSON IN DIFFERENTIAL DIAGNOSIS: UMMASKING PHEOCHROMOCYTOMA BEHIND THE FAÇADE OF PRE-ECLAMPSIA

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ABSTRACT Pheochromocytoma is a tumor of the adrenal medulla which secretes massive amounts of catecholamines. Pheochromocytoma in pregnancy poses significant risks due to potential hypertensive crises. Timely diagnosis, management, and multidisciplinary care are crucial for maternal and fetal well-being. In this case we present an antenatal woman, admitted in view of Missed Abortion with Uncontrolled Hypertension, on evaluation diagnosed to be pheochromocytoma and it's further management.

KEYWORDS : Pheochromocytoma, Uncontrolled Hypertension, Pregnancy, Missed Abortion, Adrenal, Pre-eclampsia

INTRODUCTION

Pheochromocytomas is a tumour of the adrenal medulla that secretes catecholamines leading to hypertensive crises, which may be fatal. (1) Its occurrence among individuals with hypertension is 0.2%, while it affects 0.002% of pregnancies. (2)

It has harmful effect on both mother and fetus, and can even be a life-threatening condition if the diagnosis is missed or mismanaged. Identifying pheochromocytoma during pregnancy is challenging due to its nonspecific symptoms, which can resemble those of pre-eclampsia and other pregnancy-related issues. Therefore, the management of pheochromocytoma is a great challenge to healthcare providers. Early detection and appropriate treatment of this condition can significantly reduce fetal and maternal morbidity and mortality rates from approximately 50% to lesser than 15% and 5%, respectively. (3)

CASE REPORT

A 25-year-old woman, Gravida – 2, Parity – 1, Live – 0, of 7 weeks gestational age was admitted at Sree Balaji Medical College and Hospital, Chennai in view of Missed Abortion. She had been newly diagnosed with Hypertension and was on treatment with tablet Labetalol 100 mg BD for the same. She also had complaints of headache radiating to the neck, palpitations, nausea and vomiting. Patient had history of complaints of persistently elevated Blood Pressure with blurriness of vision and headache in previous pregnancy and termination of pregnancy was done at 32 weeks with Emergency preterm Lower Segment Caesarean Section at a hospital in Patna in view of Pre-Eclampsia. Post delivery the patient continued anti-hypertensive medication for 2 months and then stopped. Unfortunately, the baby died 2 days after birth due to Respiratory Distress Syndrome.

After admission, with oral anti-hypertensives her blood pressure (B.P.) was under control. On Ultrasound – a well-defined iso-echoic lesion with few hyperechoic foci within, in right hepatorenal pouch superior to right kidney – possibly of adrenal origin was seen. Medical Method of Abortion was proceeded without any complications. Proceeding with a multidisciplinary approach, Medicine opinion was obtained and a CECT Abdomen was done to further evaluate the adnexal lesion. On CECT Abdomen (Image 1, 2), in the right adrenal gland a well-defined, mildly enhancing soft tissue density lesion shows absolute wash out of 70% and relative washout of 44%-features – of size 4.1 x 3.8 cm - suggestive of right adrenal adenoma was observed.

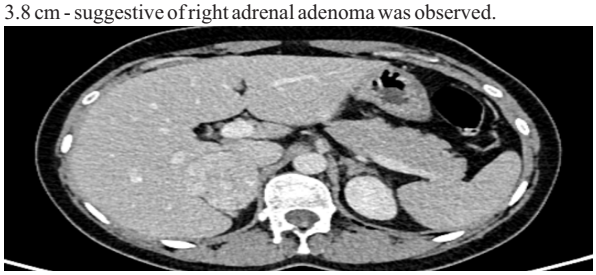

Image – 1 CE – CT abdomen (axial) showing Right Adrenal Gland lesion

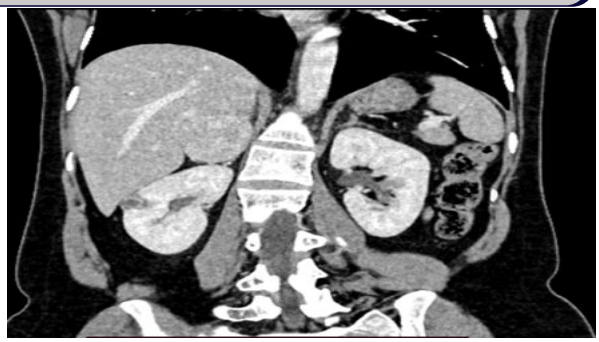

Image – 2 CE – CT abdomen (coronal) showing Right Adrenal Gland lesion

Endocrinologist opinion was obtained, with 24-hour urine metanephrine (108.54 µg/ml), 24-hour urine normetanephrine (5696.25 µg/ml), Plasma metanephrine (44.6pg/ml) and Plasma normetanephrine (110 pg/ml) and 68GA-DOTATATE PET scan (Image 3, 4) showing enlarged relatively well-defined lesion measuring 49 x 39 x 44 mm (AP x TR x CC) involving the right adrenal gland, SSTR expressing enlarged relatively well-defined lesion involving the right adrenal gland, the diagnosis of pheochromocytoma was confirmed.

Image 3: 68GA-DOTATATE PET scan – axial view

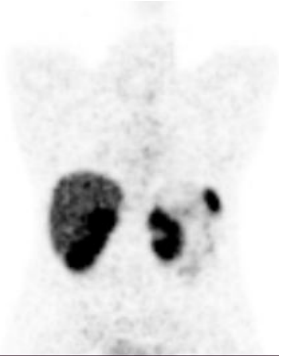

Image 4: 68GA-DOTATATE PET scan – coronal view

The patient was treated with Robotic Right Adrenalectomy under the Department of Urology and post operative hypotension and hypoglycemia was managed with inotropes and IV fluids.

On Histopathology, Macroscopy - Right adrenalectomy specimen weighing 54 gram and measuring 7 x 5 x 3.5cm. External surface, capsule was intact, showed a stapled area measuring 0.5cm. Cut surface showed yellow brown tumour measuring 4.8 x 4.2 x 3cm.

Microscopy – Sections from adrenal showed a well defined neoplasm composed of cells arranged in Zellballen pattern (nests), trabeculae and occasional sheets. Individual cells are moderate to large sized, have abundant amounts of pale eosinophilic, finely granular cytoplasm, round to oval nuclei with stippled/vesicular chromatin and scattered conspicuous nucleoli. Occasional intranuclear inclusions are noted. Occasional hyaline globules are seen. The cellular nests are invested by sustentacular cells/capillaries. Occasional multinucleated cells and cells with Bizarre nuclei (?degenerative atypia) are noted. There is no necrosis. Mitosis sparse (less than 1%). There is no capsular/ vascular/ periadrenal adipose invasion. There is no evidence of cellular spindling/ marked nuclear pleomorphism/ diffuse growth pattern There was no evidence of any ganglioneuromatous component. Peri-adrenal brown adipose tissue is noted with congested blood vessels. (Image 5,6)

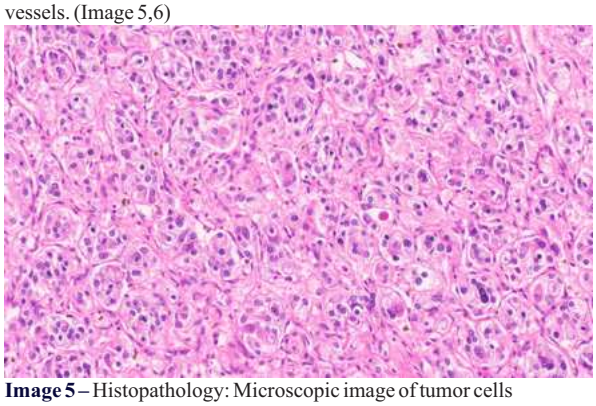

Image 5 – Histopathology: Microscopic image of tumor cells

Thereby, histopathology further confirmed the reports of Pheochromocytoma.

Patient was followed up, and she spontaneously conceived again within 3 months of the treatment. This pregnancy was uneventful, with no episodes of elevated blood pressure, headache, and blurriness of vision. She gave birth to a healthy baby at term via an Elective Repeat Caesarean Section.

DISCUSSION

Pheochromocytoma is a rare but possibly lethal neuroendocrine tumour arising from chromaffin cells of the adrenal medulla or sympathetic ganglia. These tumours typically secrete catecholamines such as epinephrine, norepinephrine, and dopamine, leading to episodic or sustained hypertension and a myriad of other symptoms. Despite its rarity, early recognition and proper management are essential due to the risk of hypertensive crises and associated complications.

The tumours can have familial or sporadic origin. Based on a recent study, there may be an association with hereditary disease-causing mutations in upto 35% cases. (4) Pheochromocytomas can also occur as part of hereditary syndromes such as neurofibromatosis type 1 (NF1), multiple endocrine neoplasia type 2 (MEN2), Hippel-Lindau (VHL) syndrome, and familial paraganglioma syndromes. While most cases are benign, approximately 10% are malignant and can metastasize to distant sites.

Symptoms of pheochromocytoma are highly variable and may include paroxysmal or sustained hypertension, palpitations, headaches, diaphoresis, pallor, and anxiety. These symptoms often occur in episodic "attacks," triggered by physical activity, emotional stress, or even changes in body position.

In the suitable clinical context, diagnosing pheochromocytoma involves confirming the hypersecretion of metanephrines and catecholamines through biochemical testing. Most recent guidelines from the Endocrine Society, suggest that plasma-fractionated metanephrines or urinary-fractionated metanephrines should be included in the initial biochemical assessment.

Subsequently, upon biochemical test indications of pheochromocytoma, the next stage of evaluation is tumor localization through radiological imaging studies.Per guidelines, the recommended initial imaging test to locate the tumour is CT scan of the abdomen and pelvis. Magnetic Resonance Imaging serves as a viable substitute for CT scans, especially when minimizing exposure to radiation or contrast is a priority, despite its slightly inferior spatial resolution. For metastatic disease, the suggested approach is 18F-FDG PET scanning. However, for situations involving radiotherapy with 123I-MIBG, the 123I-MIBG scan serves as an alternative. (5) 68Ga-DOTATATE PET/CT demonstrates greater sensitivity in detecting pheochromocytoma compared to 131I-MIBG (for both primary and metastatic lesions) and contrast-enhanced CT (for metastatic lesions). Its sensitivity is comparable to that of 18F-FDG PET/CT for both primary and metastatic lesions. (6)

Treatment of pheochromocytoma primarily involves surgical resection, with preoperative management utilizing alpha-blockers like phenoxybenzamine to control hypertension. Beta-blockers may be added cautiously to manage tachycardia once alpha-blockade is established. Laparoscopic adrenalectomy is the preferred surgical approach for localized tumours, offering reduced morbidity. In cases of metastatic or unresectable disease, systemic therapies such as chemotherapy, radiotherapy, and targeted molecular therapies may be considered. (7)

In our patient, there was an overlap between the signs and symptoms of Pre-Eclampsia in her earlier pregnancy, which lead to misdiagnosis of Pre-Eclampsia and Pre-term termination of that Pregnancy. Hence it is imperative to understand the differentiating features between the two.

Pheochromocytoma v/s Pre-Eclampsia – Differentiation (8)

Features	Pheochromocytoma	Preeclampsia
Signs and symptoms		
Time of presentation	Any trimester of Preganacy	After 20 weeks of gestation
Hypertension	Paroxysmal Orthostatic	Sustained
hypotension	Present	Absent
Bipedal edema	Absent	May be present
Headaches	Present	Usually in severe pre-eclampsia
Flushing	Present	Absent
Palpitations	Present	Absent
Weight gain	Absent	Present
Abdominal pain	Absent	Present
Laboratory findings		
Proteinuria	Often absent	Present
Glucose	Increased	Normal
Liver transaminases	Normal	Increased
Catecholamines	Increased	Normal
Thrombocytopenia	Normal	May be present

Differentiating pheochromocytoma from pre-eclampsia in pregnancy is crucial due to their overlapping symptoms. Mistaking pheochromocytoma for pre-eclampsia may lead to initial treatment for the latter, delaying the diagnosis of pheochromocytoma, which could have fatal consequences.

The treatment protocol for pheochromocytoma in pregnancy typically involves a multidisciplinary approach and careful management to ensure the safety of both the mother and foetus.

In managing pheochromocytoma during pregnancy, controlling blood pressure and preventing sudden fluctuations are paramount. Achieving a delicate balance between vasodilation and vasoconstriction is essential to optimize uteroplacental circulation, thus preventing fetal demise and avoiding impaired fetal growth. This management strategy prioritizes keeping the blood pressure in normal range and the prevention of abrupt changes in blood pressure to ensure maternal and fetal well-being. (9)

Definitive treatment is surgical resection.(10) Avoiding surgery during

the first trimester is advisable due to incomplete organogenesis, which increases the risk of miscarriage. Similarly, surgery in the third trimester is discouraged because the gravid uterus limits abdominal access and visualization. Therefore, the second trimester is considered the optimal time for surgical treatment in cases of pheochromocytoma during pregnancy. Surgical removal of the pheochromocytoma is advised before 24 weeks of gestation. [11]

CONCLUSION

Even though among hypertensive patients especially during pregnancy pheochromocytoma is a rare diagnosis, our case emphasises the significance of differentiating Pre-eclampsia and Pheochromocytoma and the need of a multi - disciplinary approach for good maternal and fetal treatment outcomes.

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