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CASE REPORT

Paraganglioma in Pregnancy with Recurrent Pregnancy Loss: A Case Report

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Abstract

Due to its rarity, pheochromocytoma or paraganglioma (PPGL) in pregnancy is often not timely diagnosed, thus resulting in high materno-fetal complications. We report a 28-year-old female who presented with paroxysmal symptoms and severe hypertension during early pregnancy. Biochemical confirmatory tests and localization imaging were delayed due to multiple factors. She suffered from two pregnancy losses before she had resection of the paraganglioma.

Key words: paraganglioma, pheochromocytoma, pregnancy, catecholamine, fetal demise

INTRODUCTION

Pheochromocytomas are rare but treacherous neuro-endocrine tumours arising from adrenal medullary chromaffin cells, while paragangliomas are mainly from extra-adrenal sympathetic or parasympathetic chromaffin tissues. Pheochromocytoma or paraganglioma (PPGL) in pregnancy is rare, with estimated incidences varying between 1 in 15,000 and 1 in 300,000 pregnancies.[1] The majority of mothers with functioning PPGL in pregnancy were symptomatic, with more than 75% presenting with hypertension in early pregnancy, allowing antepartum detection.[2] A high index of suspicion and prompt diagnosis are essential for timely management by a multi-disciplinary team to prevent disastrous maternal and fetal complications.

CASE

A 28-year-old female was first admitted on her ninth week of period of amenorrhea (POA) with a complaint of worsening headache and vomiting. During admission, her systolic blood pressure was 200 to 220 mm Hg, and her diastolic blood pressure was 100 to 130 mm Hg. Despite adequate hydration, she remained tachycardic with the highest documented pulse rate of 170 beats per minute. She reported intermittent chest heaviness, palpitation and unprovoked nervousness for the past few months. She was treated with labetalol 300 mg thrice daily, aspirin 100 mg OD and haematinics. She had no known comorbidities and was a non-smoker and teetotaller, with no significant family history of hypertension in the young or inheritable diseases.

Clinically, she had no syndromic features, and her body mass index was 20.3 kg/m^2. Blood cell counts, electrolytes and functional parameters for the liver, kidneys and thyroid were normal. Normal echocardiogram with ejection fraction of 65% excluded coarctation of the aorta or intracardiac shunts. Urine analysis was negative for albumin, red cells and casts. A 24-hour urine excretion of fractionated metanephrines confirmed a raised normetanephrine excretion of 4.2 umol/day [N: <2.13 umol/day]. Urine metanephrine excretion of 0.2 umol/day (N: <1.62 umol/day) and 3-methoxytyramine excretion of 0.4 umol/day (N: 0.1 – 1.79 umol/day) were both normal. Renal Doppler ultrasound reported normal-sized kidneys without arterial stenosis but noted the presence of a suspicious solitary left paraaortic lesion. She was at 15 weeks of gestation and refused computed tomography (CT) imaging for further assessment.

A detailed fetal scan by a feto-maternal specialist at 19 weeks of gestation reported early-onset intrauterine growth restriction with reversed end-diastolic flow on the umbilical artery and middle cerebral arterial. Serial charting on the fetal growth chart showed alarming downward percentile-crossing (Figure 1). Repeated fetal scan at 24 weeks confirmed fetal demise. She underwent second-trimester termination of pregnancy with gemeprost (Cervagem). Psychiatric expert input was sought to help her cope with the traumatic period. Postpartum, her blood pressure

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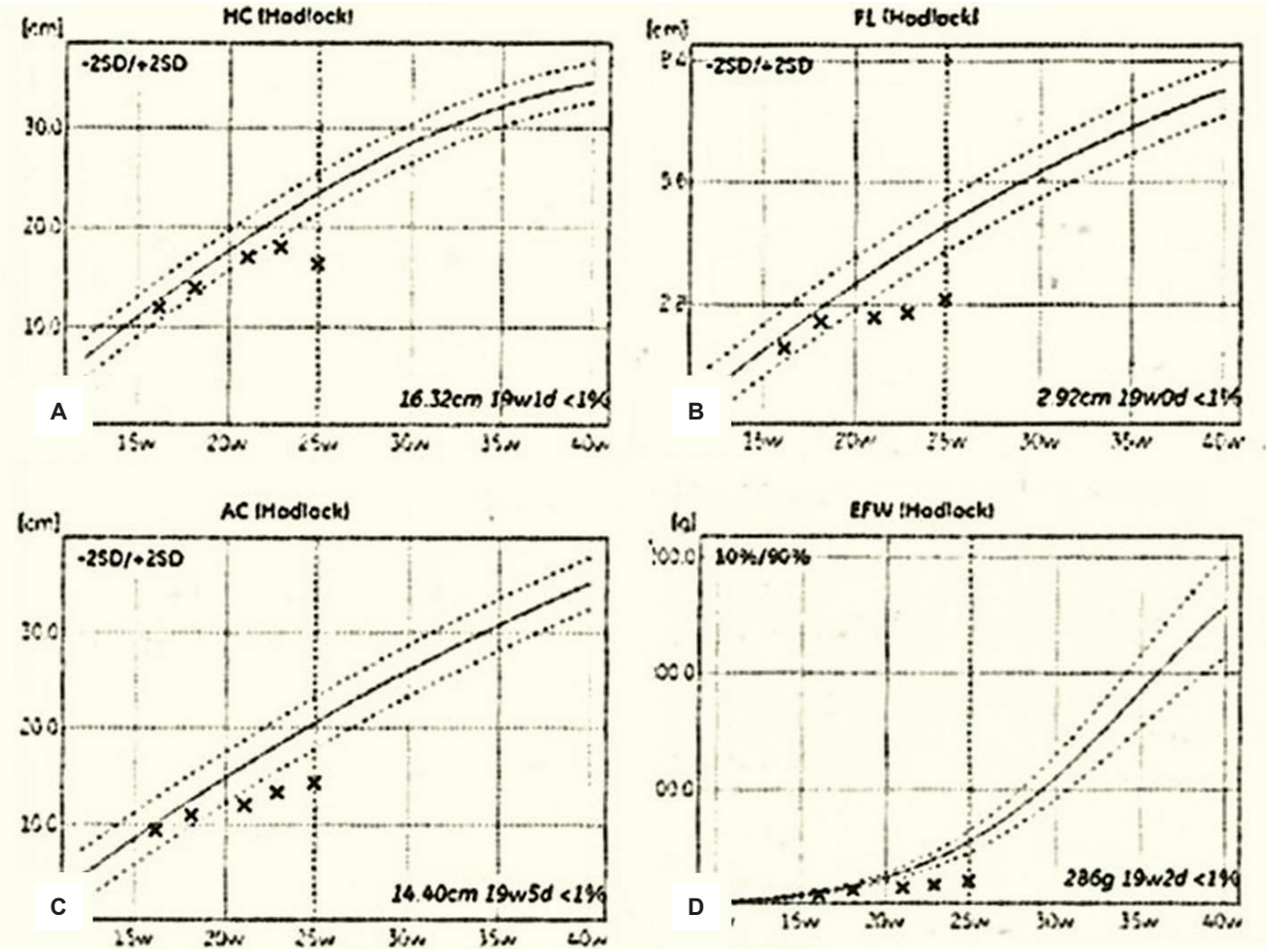

Figure 1. Fetal growth chart for first pregnancy. **(A)** HC – Head circumference; **(B)** FL – femur length; **(C)** AC – Abdominal circumference; **(D)** EFW – estimated fetal weight.

remained labile, ranging from 110 to 182 mm Hg systolic and 86 to 115 mm Hg diastolic.

Subsequently, a contrasted CT scan localized well-defined heterogeneously enhancing retroperitoneal mass or para-aortic lesion measuring 3.6 cm x 4.3 cm x 3.4 cm (AP x W x CC). The iodine-131 metaiodobenzylguanidine (^{131}I-MIBG) scan confirmed the increased tracer uptake at the medial aspect of the left paraaortic mass consistent with the CT scan findings (Figure 2). Unexpectedly, she had a positive urine pregnancy test three weeks later, with an abdominal ultrasound confirming eight weeks of pregnancy. She was on a barrier method of contraception after the first pregnancy loss. Retrospectively, she was already in early pregnancy when she had the MIBG scan, although the urine pregnancy test was negative on the day of the scan.

The nuclear medicine physician, endocrinologist and obstetrician conducted a multidisciplinary meeting amongst themselves. Concerns about radioactive exposure in early pregnancy and risk of pregnancy loss with an unresected paraganglia were discussed. The couple decided on elective termination of the second pregnancy. An intrauterine contraceptive device (IUCD) was inserted after pregnancy termination. She was prescribed phenoxybenzamine, which was titrated up to 20 mg TDS, bisoprolol 5 mg OD and amlodipine 5 mg OD to achieve a target BP of 130/80 mm Hg and heart rate of 80 beats/min prior to her scheduled left paraaortic paraganglioma excision.

During anaesthetic induction, there were BP fluctuations with the highest reading of 171/111 mm Hg and pulse rate of 99 beats/min. A well-encapsulated left paraaortic paraganglioma measuring 5 cm x 5 cm near the bifurcation of inferior mesenteric arteries (IMA) was identified and resected (Figure 3). After tumour removal, she became hypotensive with 66/37 mm Hg, requiring noradrenaline infusion, attributing it to a bleeding from the small IMA tear with an estimated blood loss of 400 ml. Noradrenaline support was discontinued 4 hours post-surgery. She remained normotensive and normoglycemic in the intensive care unit. The histopathological report confirmed extra-adrenal paraganglioma with Ki67 proliferative index of 2% and Grading system for Adrenal Pheochromocytoma and Paraganglioma (GAPP) score of 3. Succinate dehydrogenase (SDHB) immunohistochemical staining was performed and showed retained staining.

Table 1. Comparison on pertinent parameters before and after paraganglioma resection

	Before resection	6 months post resection
Main symptoms	Headache, palpitation, unprovoked nervousness	Intermittent headache
BP range	200-220/100-130 mm Hg	112-128/80-86 mm/Hg
Medications	Phenoxybenzamine 20 mg TDS Bisoprolol 5 mg OD Amlodipine 5 mg OD	None
24 hours urine metanephrine		
Normetanephrine (<2.13 umol/L)	4.2 umol/L (1.97x ULN)	0.20 umol/L
Metanephrine (<1.62 umol/L)	0.2 umol/L	0.10 umol/L
3-Methoxytyramine (<1.79umol/L)	0.4 umol/L	0.20 umol/L

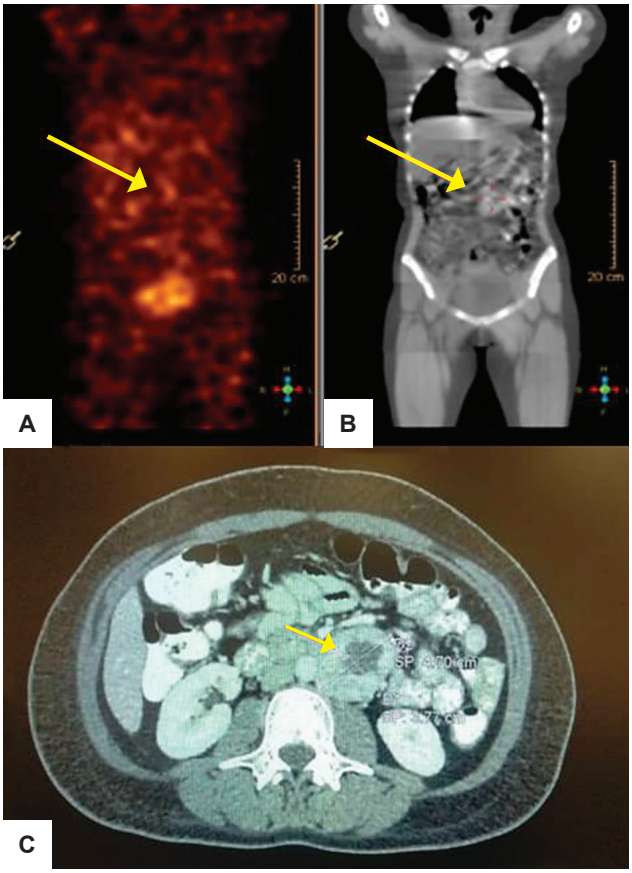

Figure 2. (A, B) ^{131}I-MIBG scan faint focal increased tracer uptake *(yellow arrows)*; **(C)** Cross Section CECT abdomen. Well-defined enhancing mass with central hypodensity at the left para-aortic region *(yellow arrow)*.

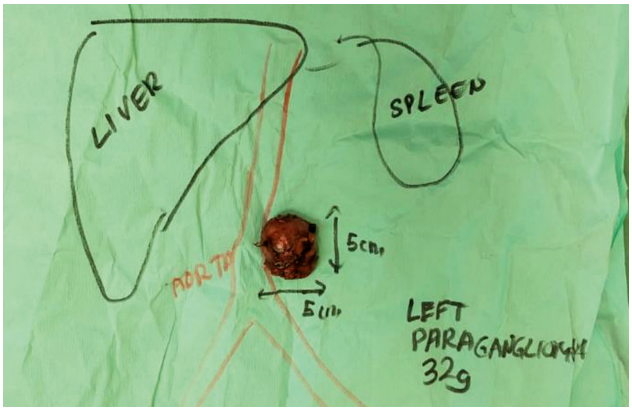

Figure 3. Left paraaortic paraganglioma resected.

Postoperatively, she was well without antihypertensive medication. 24-hour urine metanephrine repeated post-operatively was normal (Table 1). We recommended genetic testing for long-term prognostication. She was co-managed with an obstetrician to optimally prepare for subsequent pregnancies.

DISCUSSION

Diagnosing PPGL in pregnancy requires a high index of suspicion as it is rare but a significant cause of secondary hypertension in pregnancy. Mothers were mostly treated as pregnancy-induced hypertension or pre-eclampsia until recurrent admissions raised suspicion to workup for secondary hypertension (Figure 4). The overlapping features between pre-eclampsia and pheochromocytoma cause a delay in the diagnosis of PPGL in pregnancy.[3] Sustained hypertension diagnosed beyond 20 weeks of gestation associated with milder headache, pedal oedema, proteinuria and liver transaminitis will favour preeclampsia.[3] On the contrary, PPGL should be considered if mothers had paroxysmal hypertension with severe headache, flushing, palpitation and worsening glucose control.[3]

In a large case series of 249 pregnancies with PPGL, they were diagnosed during pregnancy in 134 (54%) patients at a median of 24 weeks gestation.[4] Two-thirds of reported PPGL in pregnancy were unilateral pheochromocytomas, while paragangliomas were primarily localized in the abdominopelvic area.[2,4] Functioning PPGL with higher metanephrine levels leads to more florid signs and symptoms, thus facilitating earlier suspicion and detection. Like our patient, most of them do not have relevant family history.

Fetal mortality was devastatingly high at 54.4% back in the 1970s,[5] but with increasing awareness and early treatment, pregnancy outcomes had improved significantly. In the two systemic reviews, maternal mortality was 4 to 9%, and fetal mortality was 7 to 14% if the condition was diagnosed antepartum.[2,4] However, if left undiagnosed and untreated, maternal and fetal mortality will increase to 29.3% and 25%, respectively.[2]

Excess catecholamine state can cause substantial dysregulation of physiological systems, leading to detrimental multisystemic effects. Pregnancy is a stressful state with

multiple hormonal changes that may worsen the PPGL course of disease. These changes, coupled with the growing fetus in pregnancy, may precipitate acute catecholamine crisis, especially those with abdominopelvic functioning PPGL (Figure 5). However, the placenta acts as a protective barrier for the fetus from the high maternal catecholamine level. Monoamine oxidase and catechol-o-methyltransferase (COMT) activity in the placenta will metabolically inactivate high circulating maternal catecholamine.[6] Dahia et al., found that the cord blood norepinephrine level of a fetus delivered by a mother with pheochromocytoma was only 7% of the mother's norepinephrine level.[7] Thus, fetal compromise is possibly due to haemodynamic changes in the placenta.[7] High circulating maternal catecholamine will induce a profound vasoconstrictive effect on maternal uterine arterial circulation.[8] This effect, coupled with blood pressure fluctuations, will further compromise uteroplacental circulation.[8] Reversed flow on the umbilical

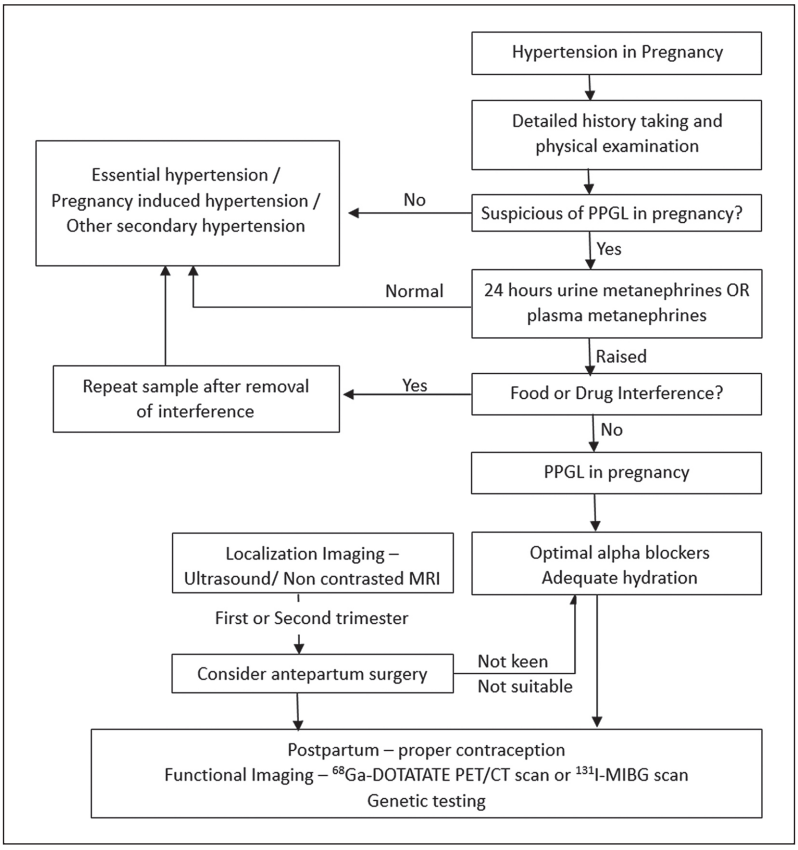

Figure 4. Algorithm of workup for of PPGL in pregnancy.

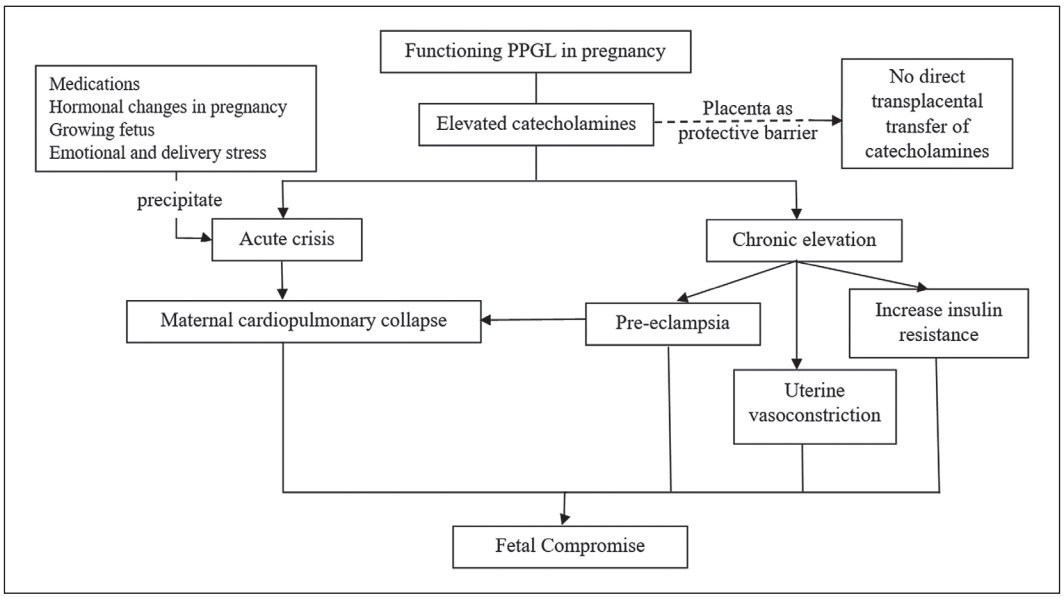

Figure 5. Conceptual framework on effect of functioning PPGL in pregnancy on fetus.

artery, as seen in our patient, is a strong indicator of placental insufficiency, which may translate into stunted fetal growth and eventually, intrauterine death.[9]

Most of the untreated PPGL were diagnosed in primigravida who are otherwise young and healthy.[4] Unfortunately, our patient had her second pregnancy before definitive resection. Elective termination of pregnancy is rarely an option and should only be considered after a multidisciplinary discussion on maternal or the problematic location of pelvic and bladder paragangliomas.[10] Our patient requested the termination of the unplanned pregnancy as she was psychologically stressed from the traumatic first pregnancy and wished for an optimal health condition before embarking on another pregnancy. Furthermore, there was radioactive exposure in early pregnancy when ^{131}I-MIBG was done. Although ^{123}I-MIBG is preferable to ^{131}I-MIBG due to lower energy photon emission and, thus, lower patient radiation, it is not yet available in Malaysia.

CT scan is essential for anatomical localization of PPGL, but radiation exposure is a major concern in pregnancy. Non-contrasted magnetic resonance imaging (MRI) is preferred.[11] Functional studies with various radioisotopes similarly have drawbacks of radioactive risk. ^{68}Ga DOTATATE PET/CT scan has higher sensitivity, higher spatial resolution and lower effective radiation dose, thus superior to ^{131}I-MIBG.[12,13] Radioactive iodine used in MIBG readily crosses the placenta, has a half-life of 8 days and emits gamma rays directly to the maternal bladder to the uterus and embryo.[11] For mothers who were found pregnant after radioactive exposure, it is important to consult medical physicists to estimate in-utero-induced deterministic radiation effects based on the gestation age and reasonable estimate of the absorbed radiation dose.[14]

Genetic testing has revolutionized the precision and holistic management of PPGL, but cost and limited accessibility are the common conundrums faced.[15] Thus, immunohistochemical staining of the tumour is slowly paving its way into clinical practice. SDHB immunohistochemistry had a sensitivity of 94.23% and specificity of 86.67%[16] to screen for SDH gene mutation. The immunoreactivity will be lost in a patient with SDH gene mutation.[16] Thus, retained SDHB immunohistochemical stain in our patient's tumour slides is relieving. Despite that, it is recommended that she be screened with a full PPGL-related genetic panel to facilitate long-term prognostication. Defining her genetic predisposition will allow proper pre-pregnancy genetic counseling.

After two unfortunate fetal losses, our patient was co-managed with an obstetrician team for contraception. Multidisciplinary discussion revealed that surgical resection is the key management.[1] Our patient achieved clinical and biochemical resolution following complete resection of the paraaortic lesion. At least ten years of follow-up is recommended, but in higher-risk patients, lifelong follow-up should be considered.[15] Younger age, larger tumours, familial disease and extra-adrenal tumours are predictors of high recurrence risk[17] No specific guideline recommends the optimal time interval between paraganglioma resection and the subsequent pregnancy. Regardless, proper preparation and close monitoring throughout the next pregnancy shall result in favourable pregnancy outcomes.

CONCLUSION

PPGL in pregnancy is a rare neuroendocrine tumour with potentially deleterious pregnancy outcomes. We reported a 28-year-old female who suffered two pregnancy losses due to PPGL in pregnancy. Early detection and multidisciplinary collaboration are essential. Prior to complete resection and biochemical remission, proper contraception should be emphasized.

Ethical Considerations
Patient consent was obtained before the submission of the manuscript.

Statement of Authorship
All authors certified fulfilment of ICMJE authorship criteria.

CRediT Author Statement
WMC: Conceptualization, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Funding acquisition; **ZH:** Conceptualization, Resources, Data Curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Funding acquisition.

Author Disclosure
The authors declared no conflict of interest.

Data Availability Statement
No datasets were generated or analyzed for this study.

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