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Successful delivery in the setting of *SDHB* metastatic paraganglioma

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Summary

Pregnancy in the setting of metastatic paraganglioma is challenging, particularly in the context of tyrosine kinase use. We describe a 26-year-old female with a background of metastatic paraganglioma harboring a pathogenic *SDHB* variant, requiring sunitinib, which was withheld to facilitate the safe conception and delivery of a healthy baby. She required no alpha- or beta-blockade during her pregnancy and exhibited no signs of tumor progression or symptoms throughout this period. Historically, higher rates of fetal and maternal morbidity and mortality have been experienced in the setting of pregnancy. Although limited data exist on the management of metastatic paraganglioma in pregnant patients, this case suggests that careful treatment modifications, such as temporary tyrosine kinase therapy cessation and vigilant monitoring, can result in successful pregnancies without compromising maternal or fetal well-being.

Learning points

- Paraganglioma in pregnancy has been associated with poor fetal and maternal morbidity and mortality.
- Many of the treatment modalities for metastatic paraganglioma, including tyrosine kinase inhibitors, can affect fertility or cannot be utilized in pregnancy, necessitating the temporary suspension of these treatments.
- This case exemplifies that careful clinical and biochemical monitoring during pregnancy is required to avoid maternal and fetal harm while balancing the risk of disease progression off treatment.

Background

Paragangliomas are extra-adrenal neuroendocrine tumors derived from autonomic paraganglia, while phaeochromocytomas arise from chromaffin tissue in the adrenal medulla. Metastatic paraganglioma/phaeochromocytoma (PPGL) occurs in 10% and 40–45% case respectively (1).

Management of locally invasive disease can include surgery or local therapies such as radiotherapy; however, metastatic disease has relied on chemotherapeutics such as CVD (cyclophosphamide, vincristine, and dacarbazine), I-metaiodobenzylguanidine (I-MIBG), or ^{177}lutetium (^{177}Lu)-DOTATATE peptide receptor nuclide therapy (PRRT). More recently, tyrosine kinase inhibitor (TKI) therapy has become an available option. A meta-analysis including 160 patients supported TKI therapy use in the setting of progressive metastatic paraganglioma when examining structural response based on response evaluation criteria in solid tumours (RECIST) criteria, with a reported pooled proportion of disease control rate of 0.856 (95% CI: 0.734–0.979) (2). In particular, the first international randomized

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study in malignant progressive pheochromocytoma and paragangliomas (FIRST-MAPP) trial established sunitinib's role in this setting.

Historically, the management of metastatic PPGL in the setting of pregnancy has been associated with elevated risk of fetal and maternal morbidity and mortality. Reported rates of maternal and fetal mortality vary significantly, ranging between 4 and 17% for the former and 7 and 26 % for the latter (3, 4). There continues to be a paucity of data regarding the optimal management of those with PPGL, including metastatic disease requiring systemic therapy. We report a case of a successful delivery in a patient with metastatic paraganglioma, necessitating the suspension of sunitinib.

Case presentation

The patient initially presented at age 10 with hypertension following a protracted history of the congenital duplex left kidney associated with recurrent urinary tract infections. She was found to have raised plasma normetanephrine levels of 1.17 nmol/L (normal range: <0.5 nmol/L) and normal plasma metanephrine levels of 0.18 nmol/L (normal range: <0.9 nmol/L). A CT scan of the abdomen and a whole-body MIBG scan revealed a 4 cm right-sided, vascular-enhancing mass. This was surgically resected, and histopathology confirmed the presence of a 48 × 40 × 40 mm paraganglioma with focal sparse lymphatic invasion and disruption of the capsule.

Investigation

Annual reviews were stable until age 14 when she redeveloped headaches and was found to have elevated urinary noradrenaline levels. Repeat MIBG scanning demonstrated an L2 and L1 bony lesion as well as a paravertebral mass near the right L2 vertebra. Surgical resection was again performed, and it was confirmed to be a recurrent, metastatic paraganglioma. A section of her sixth left rib was also resected in 2012, given persistent avidity on a ^{68}Ga-DOTATATE PET scan. While this became non-avid, she continued to have DOTATATE avid disease of her right T8 pedicle, L1 vertebral body, L3 vertebral hemibody, left second rib, left anterior iliac bone, and left frontal skull bone. She was largely asymptomatic of these lesions, reporting mostly mild headaches.

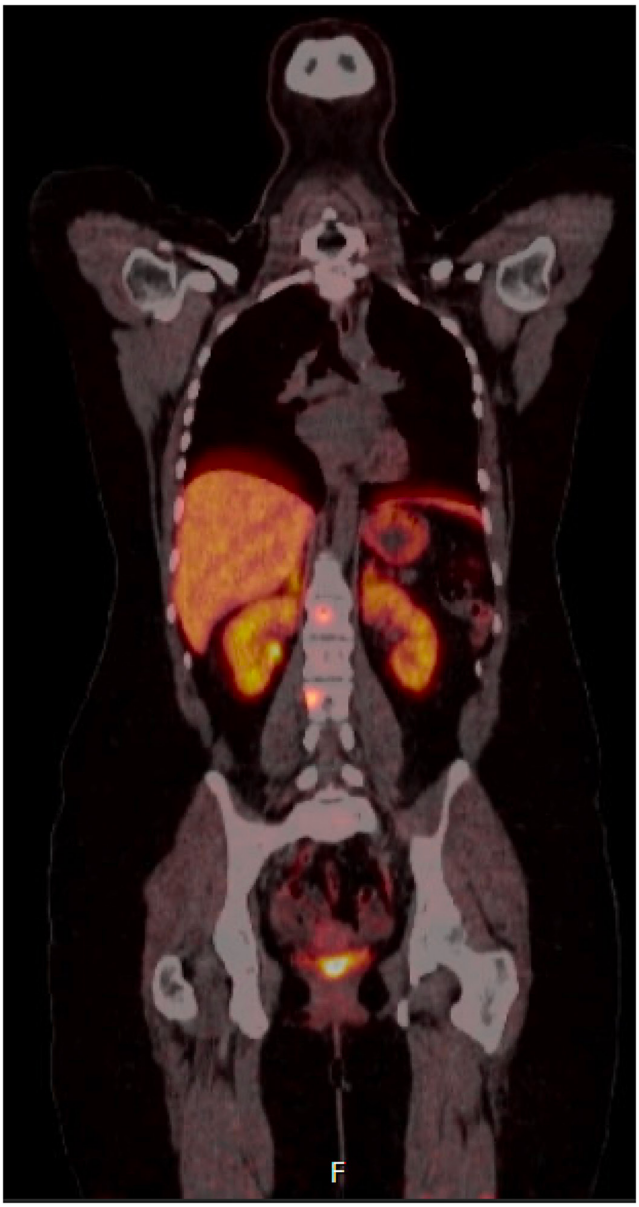

Figure 1

Pre-pregnancy ^{68}Ga DOTATATE PET scan.

Genetic testing was performed to investigate germline abnormalities, and a pathogenic variant c.587G>A, p.Cys 196Tyr (C196Y) in exon 6 of the *SDHB* gene was detected. Her younger sister, father, paternal uncle,

Table 1 Screening hormone levels.

Hormone	Preconception	Second trimester	Third trimester	Normal range
24 h urine normetanephrine, µmol/day	2.1	2.2	3.8	<2.3
24 h urine metanephrine, µmol/day	0.3	0.5	0.5	<1.7
24 h urine 3- methoxytyramine, µmol/day	0.7	0.7	1.2	<1.3
Plasma normetanephrine, pmol/L			730	<570
Plasma metanephrine, pmol/L			<50	<447
Plasma 3- methoxytyramine, pmol/L			<50	<181

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and paternal grandmother harbor the *SDHB* variant with no disease.

Due to persistent metastatic disease, she underwent four cycles of PRRT with ^{177}lutetium-DOTA-octreotate from the age of 15–16 years. Despite this, she developed new DOTATATE-positive bony lesions. At age 16, she was commenced on a high dose of sunitinib 50 mg daily, however, this was complicated by renal failure, ascites, and bilateral pleural effusions, necessitating a prolonged hospital admission. Following the resolution of these complications, sunitinib was reintroduced at a lower dose of 25 mg for 28 days with 14 days off the drug. Repeat DOTATATE imaging demonstrated her disease remained stable, affecting her left frontal skull, left mandibular ramus, right T8 and L1, L3 vertebral body, and left iliac wing. Amlodipine 10 mg daily was commenced for the management of hypertension. Her major reported side effects included lethargy, malaise, hyperesthesia of her hands and feet, and mild nausea.

Treatment

She was referred to a reproductive endocrinologist as the patient and her partner wished to conceive with their own gametes when she was 24 years old. There were concerns regarding the adverse effects of prior treatment on her ovarian function and oocyte quality. In preparation for mature oocyte collection for cryopreservation, sunitinib was discontinued for 6 weeks. She tolerated a short period of general anesthesia for transvaginal US-guided follicle aspiration with no catecholaminergic crisis. She developed a new low-grade bony lesion at T11 off sunitinib and became symptomatic with left hip pain at the site of her left ileum metastasis; otherwise, her other disease sites remained stable. Pre-implantation genetic testing was considered, given the autosomal dominant pattern of inheritance of *SDHB*-associated PPGL; however, this was not completed prior to embryo transfer. Throughout 2022, she was unsuccessful with multiple trials of *in vitro* fertilization. At this stage, she had remained off sunitinib for a year with no further significant progression of disease, as demonstrated on a ^{68}Ga-DOTATATE PET scan (Fig. 1).

Outcome and follow-up

At age 25, she conceived naturally. Throughout her pregnancy, her blood pressure remained stable. On screening pathology, her plasma normetanephrines and urinary normetanephrines were mildly elevated (detailed in Table 1). She had no radiological progression of the disease. She delivered successfully via vaginal delivery with no fetal complications. She experienced 1 L postpartum hemorrhage secondary to uterine atony. A ^{68}Ga-DOTATATE PET scan completed post-delivery demonstrated stable avid osseous metastatic disease (Fig. 2). At her last follow-up, given the stability of her disease, it was decided that she should remain off sunitinib while breastfeeding. A timeline of her clinical progress on and off sunitinib is demonstrated in Fig. 3.

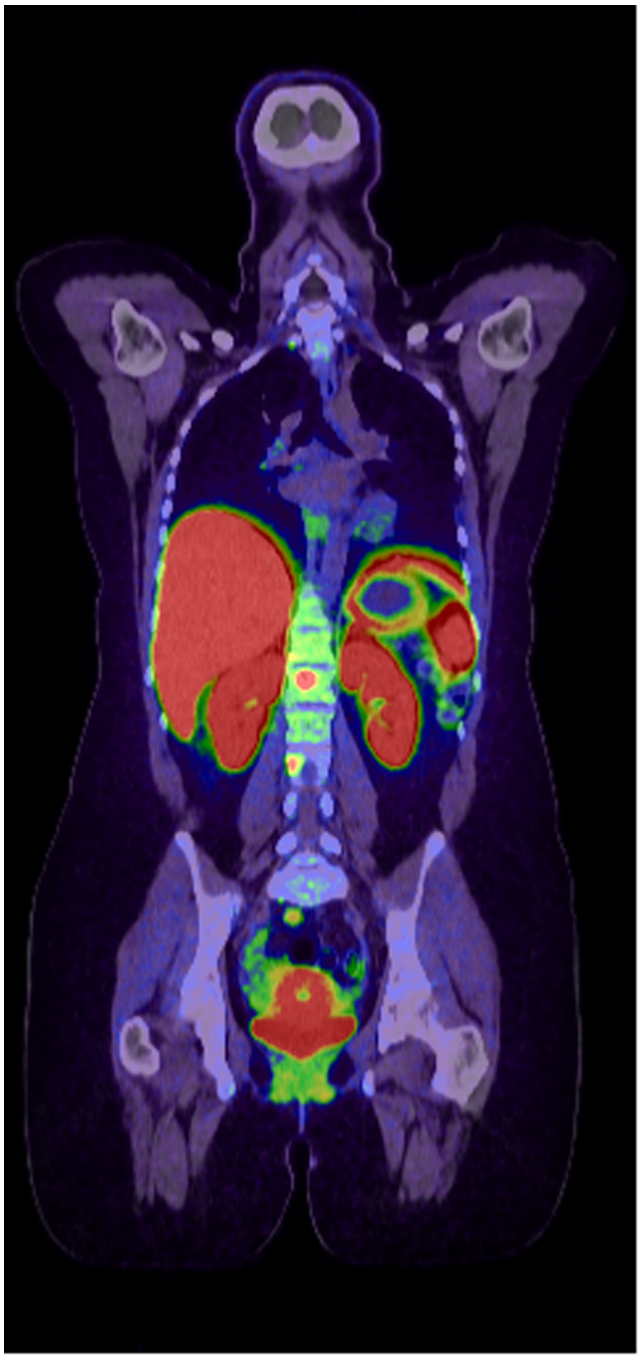

Figure 2

Postpartum ^{68}Ga-DOTATATE PET scan.

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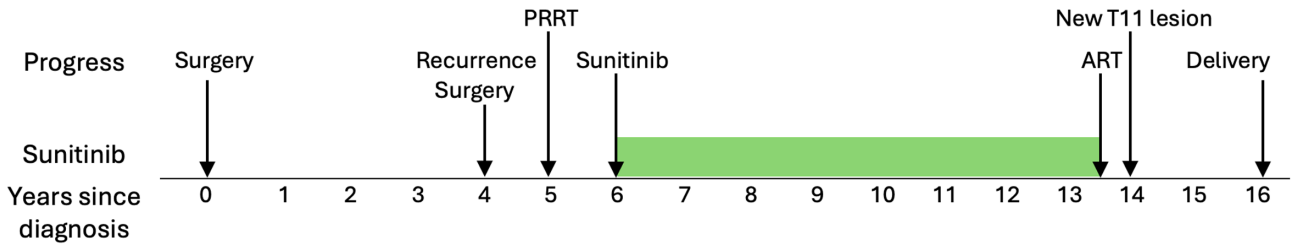

Figure 3

Timeline of clinical progress. Green shading represents the time period on sunitinib, PRRT (peptide receptor radionuclide therapy), and ART (assisted reproductive treatment).

Discussion

Metastatic paraganglioma is a rare and often aggressive neuroendocrine tumor requiring specialist management. Augmenting this with pregnancy renders it even more complicated, with the clinician balancing the health and safety of both the mother's disease and the developing fetus. There is a paucity of data and established guidelines for this specific clinical scenario, which can lead to uncertainty and anxiety for patients and healthcare providers alike. The tumor's potential to produce excess catecholamines can pose risks to the mother's cardiovascular and endocrine systems as well as the developing baby's well-being. Additionally, deciding whether to continue or suspend TKI therapy, as demonstrated in the case presented, is a complex decision that hinges on weighing the risk of tumor progression against the potential harm to the fetus.

The genetic milieu of PPGL is complex. PPGLs can occur sporadically and are associated with various syndromes including multiple endocrine neoplasia syndromes, von Hippel–Lindau disease, and neurofibromatosis type 1. *SDHx* mutations are mostly associated with the development of PPGLs. PPGLs occur in three clusters – psuedohypoxia characterized by stabilization of the hypoxia-inducible factor and increased angiogenesis (i), kinase (ii), and Wnt signaling (iii) (1, 5).

Metastatic PPGL confers a poorer prognosis; however, there is no risk stratification score or reliable predictors for determining which individuals will develop metastatic disease. Forty percent of sympathetic paragangliomas metastasize, leading to the development of areas of disease where chromaffin tissue is not normally present. Risk factors for metastatic disease include tumor size, sympathetic paraganglioma, norepinephrine secretion, higher levels of 3-methoxytyramine, and synchronous metastases (6). Certain germline mutations, including *SDHB, FH*, *MAX*, and potentially *SLC25A11* and somatic mutations TRX, TERT, or MAML3, are linked to a higher risk for metastatic disease (5). Our patient had an *SDHB* mutation and biochemically secreted normetanephrine, which likely conferred a higher risk for metastatic disease.

The mainstay management of PPGL outside of pregnancy is surgical. If this is not possible, other locoregional therapy such as radiotherapy can be considered. In the setting of diffuse or recurrent disease, systemic therapy including chemotherapy or targeted molecular therapy are potential options for treatment. Increasingly, radionuclide therapy, including ^{131}I-MIBG therapy and PRRT, is being utilized. As per the FIRST-MAPP trial, sunitinib, a TKI, has demonstrated improved progression-free survival at 12 months vs placebo in patients with progressive malignant PPGLs (35.9% vs 18.9%) (7). Sunitinib now has an established role in this setting, as seen with the case we have presented.

Managing PPGL in pregnancy is difficult, given the potential for significant maternal and fetal morbidity and mortality, which is further compounded by the limited treatment options that have proven safety data in pregnancy. In a case report review, maternal mortality rates were reported as 9% while fetal mortality was 14%. Postpartum or postmortem diagnosis was associated with 42-fold higher and 2.6-fold higher maternal and fetal mortality, respectively (8). Poorly controlled PPGL can lead to potentially fatal complications of a catecholaminergic crisis, leading to stroke, cardiovascular complications such as myocardial infarction or cardiomyopathy, or death (4). Adequate blood pressure control must be achieved during pregnancy, given the risk of placental complications and intrauterine hypoxia during catecholaminergic crises. However, this must be judicious, as studies examining women without PPGLs have demonstrated that excessive blood pressure reduction can lead to placental insufficiency and intrauterine growth restriction (9). Close monitoring of both the fetus and mother is paramount.

There is now emerging data in the setting of pregnancy and management of metastatic PPGLs. A multicenter retrospective study, including 232 women with PPGLs with 249 pregnancies examining maternal and fetal outcomes was completed (4). Of these cases, 8.7% had metastatic disease. Adverse outcomes were associated with unrecognized PPGLs during pregnancy, abdominal/pelvic location, and catecholamine levels more than 10 times the upper limit of normal. Notably, this group found that adequate medical management via alpha- and beta-blockade reduced the risk of adverse

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outcomes, while surgery did not significantly improve outcomes. Two case series published support this data, with most documented cases being managed via medical management (9, 10). One neonate required intubation post-delivery; however, this was thought to be multifactorial in the setting of sedation and the use of phenoxybenzamine for alpha-blockade (9). Notably, these cases were not on tyrosine kinase therapy, and the retrospective study further did not comment on prior TKI use.

The therapies utilized for metastatic PPGLs have been shown to have varying effects on fertility as well as different implications for safety in the setting of pregnancy. Sunitinib is a category D medication, as it has been shown to be embryotoxic and teratogenic. Thus, it cannot be continued during planned conception or pregnancy. Mouse studies have demonstrated that sunitinib exposure reduced corpora lutea per ovary and serum anti-Müllerian hormone levels (11). Treatment withdrawal facilitated mice to have successful pregnancies. There are limited data on the effects of PRRT on fertility; however, these are generally thought to be transient. There is a paucity of data on the potential long-term side effects on fertility of treatments indicated in the setting of metastatic or inoperable PPGLs.

Here, we have reported on a case of successful delivery in the setting of metastatic paraganglioma with a pathogenic variant of *SDHB*. The patient demonstrates that in certain cases, sunitinib can be safely withheld to facilitate conception and delivery, providing hope for other patients with metastatic PPGLs who wish to conceive. This case further supports current data that suggest that close monitoring and medical management are safe and optimal to manage PPGLs during delivery.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the study reported.

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Patient consent
Written informed consent for publication of their clinical details and/or clinical images was obtained from the patient.

Author contribution statement
MM wrote the primary manuscript. BR and MG assisted with conceptualization and edited the manuscript.

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