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Ga-68 DOTATATE PET/CT in the Localisation of Succinate Dehydrogenase D Subunit (SDHD) Pheochromocytoma

Abstract – Pheochromocytoma and paraganglioma (PPGLs) are neural crest derived neoplasms. More than 35% of PPGLSs are hereditary with four common subunit gene mutations including succinate dehydrogenase (SDH) complex. This is a case report of 9-year-old girl with family history of SDHD gene mutation who presented with hypertensive urgency. She was treated with non-selective alpha blocker and was then arranged for ultrasound and MRI abdomen which both are suggestive of pheochromocytoma. She was referred to Nuclear Medicine Department for staging with Ga-68 DOTATATE PET/CT. The scan showed focal Ga-68 DOTATATE uptake seen at the left suprarenal mass and another focal uptake was seen at the hypodense lesion at right level II cervical region. This case report illustrates Ga-68 somatostatin agonist as the first choice of tracer for SDHx mutation as well as head and neck paraganglioma, extra- adrenal sympathetic multifocal and/or metastatic PPGLs.

Keywords – *Ga68-DOTATATE, SDHD, pheochromocytoma*

1 BACKGROUND

Pheochromocytoma and paraganglioma (PPGL) are neural crest derived neoplasms. PPGLs occur between 0.2 to 0.6% in patients with hypertension in general outpatient clinic (1). In children with hypertension, the prevalence of PPGL is higher with approximately 1.7%.[2] Study has shown that approximately 5% of patients with incidental findings of adrenal masses on anatomical imaging are diagnosed with pheochromocytoma.[1] Approximately 5-10% of solitary pheochromocytoma are hereditary, whereas about 70% of patients with multiple pheochromocytoma or combination of pheochromocytoma with synchronous or metachronous paraganglioma are related to germline mutation (1). This case report hopes to alarm us with the use of Gallium-68 DOTATATE PET/CT in the localisation of the succinate dehydrogenase D subunit (SDHD), one of the many types of germline mutation in PPGL.

2 CASE PRESENTATION

A 9-year-old girl presented with a complaint of a four-month history of headache, sweatiness, palpitation, and weight loss. Her clinical examination was unremarkable except for her blood pressure, which was more than 99th centile during her first presentation. She was admitted and treated for hypertensive urgency.

Upon additional investigation, it was revealed that she has a significant family history of pheochromocytoma, which affected her father and paternal grandfather. The patient and her two younger siblings were identified with SDHD gene mutation, similar to their father. All other siblings are asymptomatic during this presentation. During the admission, her USG Abdomen showed left suprarenal mass measuring 3.1 x 3.4 x 4.1 cm. Subsequent MRI Abdomen showed retroperitoneal left para-aortic lesion likely arising from the left adrenal gland in keeping with pheochromocytoma with the differential of paraganglioma. Result of her urine normetanephrine was raised at 12.11 micromol/24H.

During her admission, patient was started on oral phenoxybenzamine; a non- selective alpha-blocker. Her BP was successfully controlled while on the medication. Patient was then referred to Nuclear Medicine department for staging with Ga-68 DOTA somatostatin receptor (SSTR) study. Emission and transmission scan from head to proximal thigh; starting 60 minutes post injection of the Ga-68 DOTATATE 185MBq was acquired (Figure 1). The scan showed focal Ga-68 DOTATATE uptake seen at the left suprarenal mass (SUVmax 14.5) likely to arise from the left adrenal gland measuring 2.8 x 1.9 cm on CT (Figure 2). Another focal Ga-68 DOTATATE uptake was seen at the hypodense lesion at right level II cervical region (SUVmax 21.0) measuring 1.0 x 0.8 cm on CT (Figure 3).

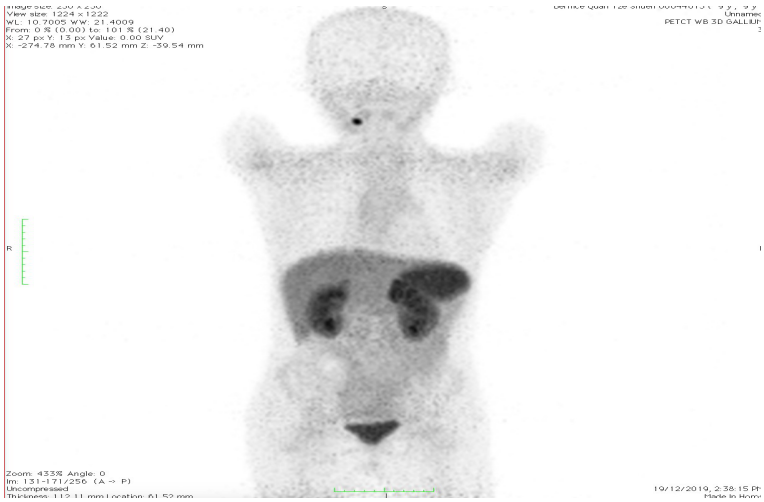

Figure 1. Maximum intensity projection (MIP) of Ga-68 DOTATATE

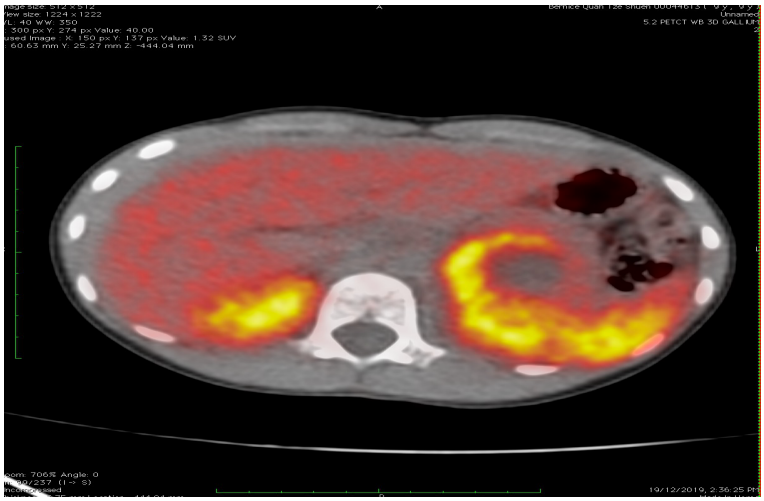

Figure 2. Focal of Ga-68 DOTATATE uptake seen at the left suprarenal mass (SUVmax 14.5) likely to arise from the left adrenal gland measuring 2.8 x 1.9 cm

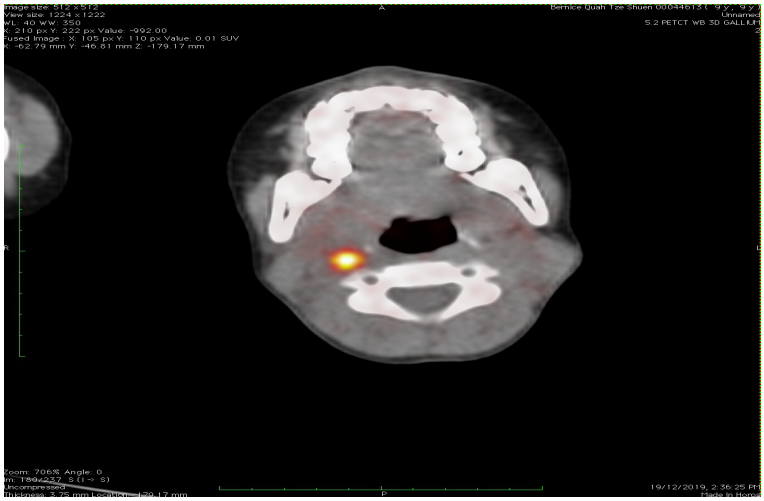

Figure 3. Focal of Ga-68 DOTATATE uptake seen at the hypodense lesion at right level II cervical region (SUVmax 21.0) measuring 1.0 x 0.8 cm on CT

On reviewing the Ga-68 DOTATATE findings, surgical team had arranged an ultrasound neck for the patient. However, the ultrasound had shown unremarkable finding likely due to the small and deep location of the right cervical lesion. They initially planned for MRI of the neck followed by HPE for confirmation of diagnosis, which is important in deciding patient's further management, but recent followed up of this case showed that MRI and HPE was not being carried out. The lymph node was concluded as a reactive lymph node, due to recent inflammation and infection.

3 CASE DISCUSSION

Pheochromocytoma is a tumour arising from the adrenomedullary chromaffin cells that produce one or more catecholamines, which include epinephrine, norepinephrine and dopamine (2). On the other hand, paraganglioma is a tumour that derived from the extra- adrenomedullary chromaffin cells of the sympathetic paravertebral ganglia of thorax, abdomen and pelvis. Paraganglioma may also arise from the parasympathetic ganglia, which usually located in head and neck as well as in the anterior mediastinum (1,2). 85% of chromaffin-cell tumours are pheochromocytoma whereas the remaining 15%-20% are paraganglioma.[2] Patient with pheochromocytoma usually presented with catecholamine over-secretion symptoms including sustained or paroxysmal increase in blood pressure, headache, profuse sweating, palpitation, pallor and anxiety (2). However, head and neck parasympathetic paraganglioma (HNPG) commonly does not secrete catecholamine and are often diagnosed incidentally during imaging or revealed only by symptoms and signs of compression to the adjacent structures (2).

More than 35% of PPGLSs are hereditary, including multiple endocrine neoplasia 2 (MEN2), von Hippel–Lindau syndrome (VHL), and neurofibromatosis 1 (NF1). In recent years, gene mutations encoding the four subunits including succinate dehydrogenase (SDH) complex, fumarate hydratase (FH), MYC-associated factor X (MAX) and hypoxia-inducible factor 2a (HIF2A) have been evaluated and often found to be associated with the presence of multiple and metastatic PPGLs (1-3). There are few risk factors found to have association with hereditary PPGLs and some which are related to our patients are diagnosis at young age, having a family history of PPGLs, presence of multifocality and the elevation of urine normetanephrine. Otherwise, other known risk factors of hereditary PPGLs non-related to our patients are by having previous history of PPGLs, unusual location of the tumour, syndromic presentation as well as tumour recurrence particularly in the adrenal gland (1,2).

Nuclear imaging plays an important role in PPGLs. Good understanding of each radiopharmaceutical used in nuclear medicine imaging for PPGLs is pivotal as each of it is different from one another by its mechanism of action on different type of receptors or transporters. Taiieb *et al*. as published in the European Journal of Nuclear Medicine in 2019 had proposed clinical algorithm for nuclear medicine investigation in PPGLs (Table 1). According to this algorithm, Ga-68 somatostatin agonist (SSA) has been suggested to be the first choice of imaging for patient with SDHD gene mutation, as per our patient. This suggestion also implies as well to HNPGL, extra-adrenal sympathetic, multifocal and/or metastatic PPGLs.[1] Furthermore, Ga-68 DOTA-SSTR PET/CT is suggested to be the most sensitive tool in the detection of HNPGLs, especially SDHD-related tumours, which may be very small in size and/or fail to sufficiently concentrate F-18 FDOPA (3-5). In relation to our case report, few studies had indicated elevated clinical value of Ga-68 DOTATATE in the paediatric population especially with SDHx mutation (3,5).

Tan *et al* in his study has proposed that although Ga-68 DOTATATE PET/CT demonstrates only marginal better sensitivity and accuracy than F-18 FDG PET/ CT on PPGL per-patient basis, Ga-68 DOTATATE PET/CT is albeit significantly superior to F-18 FDG on PPGL per-lesion basis (Table 2). Based on his study, the sensitivity of Ga-68 DOTATATE PET/CT in detecting PPGL per lesion is 91.5% compared to only 51.3% with F-18 FDG PET/CT (6). This could be due to the marked overexpression of SSTR-2 in PPGL combined with the lower background activity in Ga-68 DOTATATE which resulted in significantly superior tumour contrast thus allowing easier and more definite diagnosis (7). Identification of metastatic lesion per patient is as important as mapping all metastatic lesions accurately (6). This is supported by Janssen *et al*. who had demonstrated significantly superior detection rate of DOTATATE PET/CT in a prospective series of 17 patients with SDHB-related metastatic PPGLs compared to FDG, fluoro-dihydroxyphenylalanine (FDOPA), fluoro-dopamine (FDA) and CT/MRI. As reported by Janssen *et al,* a lesion-based detection rate of 99% was seen with DOTATATE compared to 86 % for FDG PET/CT (6). The discrepancy of sensitivity between the studies of Tan *et al* and Janssen *et al* may be related to the use of

different reference standards in validating the disease (6).

Tan *et al*. and other previous studies had also proposed that the diagnostic performance of I-131 MIBG scintigraphy in the detection of metastatic PPGLs on per- patient and per-lesion basis was rather low with only 46.7% and 15.7% respectively (Table 2). The study had highlighted that use of SPECT/CT with I-131 MIBG would be a better comparison with Ga-68 DOTATATE PET/CT and F-18 FDG PET/ CT. Therefore, it implies that I-131 MIBG is rather useful only for extra-adrenal screening in patient with initial presentation of benign PPGL or as an assessment of patient's suitability for I-131 MIBG therapy (6).

It is important to diagnose, localize and treat inherited PPGLs as most of inherited PPGLs may overly secrete the catecholamine. SDHD gene mutation in relation to our patient, if left untreated, may lead to cardiovascular morbidity and mortality. Other reason to encourage case detection is that in some familial disease, early detection of a tumour may result in earlier diagnosis and treatment in other affected family members. Some PPGLs may also have malignant potential, which defines as the presence of metastases in non-chromaffin tissue with the prevalence of between 10% to 17% (1-3). Mutations in the gene encoding SDH subunit B (SDHB) are known to lead to metastatic disease in 40% or more (1-3). Therefore, early detection of SDHB that is known to be associated with higher risk of aggressive behaviour is important among the PPGLs. Finally, different subgroups of PPGL exhibit different patterns of catecholamine secretion, as well as the cell membrane receptors and the transporter expressions. As mentioned above, the first line choice of nuclear imaging for SDHx mutation is different from the other inherited PPGLs thus emphasised the importance of identifying the subgroups of PPGLs (2).

In view of our patient's clinical history especially with a strong family history of SDHD gene mutation, her scan findings of somatostatin receptor avid primary disease in the left suprarenal mass are highly likely to be pheochromocytoma. However, the somatostatin avid disease in the right cervical region could have many probable differential diagnoses. These include head and neck extra-adrenal paraganglioma, multifocal or metastatic sympathetic pheochromocytoma, other sympathoadrenal tumours (eg. neuroblastoma or ganglioneuroma) or reactive lymph node.

Head and neck paraganglioma (HNPG) could be one of the differentials based on the location of the Ga-68 DOTATATE PET/CT uptake. The most common origin of HNPGs is the carotid body, jugular bulb, tympanic plexus nerve or vagal nerve. As previously discussed, HNPGs commonly do not secrete catecholamine but may cause symptoms and signs of compression to the adjacent structures. The first choice of treatment for HNPG is surgical removal but could be associated with high risk of morbidity (3). In patients with non- or incompletely resected large PPGL, a radiotherapeutic management could be considered and also as complementary therapy after debulking surgery(3). Surgical removal of head and neck paraganglioma could be challenging as most critical structures are located surrounding the lesion. Therefore, systemic peptide receptor radionuclide therapy (PRRT) and/or locoregional treatment with external beam radiotherapy could be a better option for those who are symptomatic (3). Few studies have suggested that PRRT using Lu-177 DOTA-SSA will be more suitable for SDHx-related PPGL than I-131 MIBG(3).

Another differential is multifocal or metastatic pheochromocytoma. Even though PPGLs are mostly benign, 30% of them are thought to be metastatic (2). There are few important factors that may contribute to metastatic PPGLs, including SDHB mutation, alpha thalassemia, mental retardation syndrome X-linked mutation, large tumour (>5cm), extra-adrenal location, noradrenergic biochemical phenotype as well as high methoxytyramine level. Patients with these important factors as per our patient may benefit from the functional imaging for staging at the initial presentation (2). On the other hand, nuclear medicine functional imaging is also useful for restaging and follow- up as it is more sensitive than the anatomical imaging in detecting tumours especially at the unusual and distant places (2). The treatment for multifocal or metastatic pheochromocytoma is similar as above, which is surgical, PRRT and/or locoregional treatment with external beam radiotherapy.

Table 1. Proposed clinical algorithm for nuclear imaging investigations in cases of pheochromocytomas and paragangliomas. Adapted from the European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of pheochromocytoma and paraganglioma

	First choice	Second choice	Third choice (if [^{18}F]FDOPA or [^{68}Ga]Ga-SSA is not available)
PHEO (sporadic)	[^{18}F]FDOPA or [^{123}I]MIBG	[^{68}Ga]SSA	[^{18}F]FDG
Inherited PHEO (except *SDHx*): *NF1/RET/VHL/MAX*	[^{18}F]FDOPA	[^{123}I]MIBG or [^{68}Ga]SSA	[^{18}F]FDG
HNPGL (sporadic)	[^{68}Ga]SSA	[^{18}F]FDOPA	[^{111}In]SSA/[^{99m}Tc]SSA
Extra-adrenal sympathetic and/or multifocal and/or metastatic and/or *SDHx* mutation	[^{68}Ga]SSA	[^{18}F]FDG and [^{18}F]FDOPA	[^{18}F]FDG and [^{123}I]MIBG or [^{18}F]FDG and [^{111}In]SSA/[^{99m}Tc]SSA

The above algorithm can be proposed as per the clinical situation. This algorithm should be practically adapted in each institution and evolve with time.

PHEO: phaeochromocytoma, [^{123}I]MIBG: iodine-123-labelled meta-iodobenzylguanidine, [^{18}F]FDA: fluorine-18-labelled fluorodopamine, [^{18}F]FDOPA: fluorine-18-labelled fluorodihydroxyphenylalanine, [^{18}F]FDG: fluorine-18-labelled fluorodeoxyglucose, [^{68}Ga]SSA: gallium-68-labelled somatostatin analogue, [^{111}In]SSA: indium-111-labelled somatostatin analogue, [^{99m}Tc]SSA: technetium-99-labelled somatostatin analogue, NF1/RET/VHL/MAX: neurofibromin 1/rearranged during transfection proto-oncogene/von Hippel–Lindau/myc-associated factor X, HNPGL: head and neck paraganglioma, SDHx: succinate dehydrogenase subunits.

Table 2. Diagnostic performance of all three modalities based on per patient and per lesion analysis. Adapted from Tan *et al.*

	^{68}Ga-DOTATATE PET/CT	^{131}I-MIBG scintigraphy	^{18}F-FDG PET/CT
Per-patient			
Sensitivity	93.3 %	46.7 %	90.9 %
Specificity[a]	100 %	100 %	100 %
Accuracy	94.1 %	52.9 %	91.7 %
Per-lesion			
Sensitivity	91.5 %	15.7 %	51.3 %
Specificity[a]	100 %	100 %	100 %
Accuracy	92.6 %	26.0 %	57.8 %

[a] Since any unequivocal lesion detected by either ^{68}Ga-DOTATATE PET/CT, ^{131}I-MIBG scintigraphy or ^{18}F-FDG PET/CT was considered true positive, the specificities of all three modalities are thus, by definition, 100 %

Take home points:

- SDHD is one of the many types of gene mutation in PPGLs.
- Ga-68 SSA is the first choice of tracer for SDHx mutation as well as HNPGL, extra-adrenal sympathetic, multifocal and/or metastatic PPGLs.
- Indication for nuclear medicine imaging in PPGLs include confirmation of a PPGL diagnosis, staging at initial presentation of PPGL, restaging and follow-up as well as selection for targeted molecular radiotherapy.
- Surgical resection is the first line of treatment in symptomatic PPGLs, however in non-complete or unresectable lesion of symptomatic PPGLs, systemic PRRT or EBRT is the alternative choice of treatment.

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