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MULTIMODALITY RADIONUCLIDE DIAGNOSTIC IMAGING FOR PERSONALISED TARGETED RADIONUCLIDE THERAPY IN PHEOCHROMOCYTOMAS AND PARAGANGLIOMAS: CASE SERIES.

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ABSTRACT:

Pheochromocytomas and paragangliomas, commonly referred to as PPGLs, are rare neuroendocrine tumours that occur in adolescents and children. It arises from the chromaffin tissue of the adrenal medulla and extra-adrenal sympathetic/parasympathetic ganglia. Its symptoms vary; but the most prominent symptom is severe hypertension, caused by the release of catecholamines produced by the tumour. Metastatic disease requires thorough evaluation using both anatomical and functional imaging modalities. Anatomical imaging includes CT and MRI play a vital role in anatomical localization, tumor characterization and surgical planning. Meanwhile, radionuclide diagnostic imaging like F^{18} FDG- PET/CT, Ga^{68} DOTATATE- PET/CT, and I^{131} meta-iodobenzyl-guanidine (MIBG) are commonly used to detect locoregional recurrence and metastatic disease localisation depending on the functional avidity of the tumour. These images findings are critical in guiding clinical decision-making. Multidisciplinary meetings plays an important role in planning personalised treatment strategies, which may include surgery, chemotherapy and targeted radionuclide therapy such as I-131 MIBG and Peptide receptor radionuclide therapy (PRRT) depends on the tumor location, extent of metastatic disease and avidity on the functional imaging. Multimodality radionuclide diagnostic imaging facilitates accurate disease assessments, optimises treatment approaches and improves prognostic outcomes. Integrating advanced imaging modalities with multidisciplinary input ensures a personalized and effective care approach for children and adolescents with PPGLs.

Keywords: Pheochromocytomas, Paragangliomas, FDG PET/CT, Ga68 DOTATATE PET/CT, MIBG scan.

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CASE PRESENTATION:

We presented 2 cases of metastatic paraganglioma seen in our centre.

The first case involved a 23-year-old lady with metastatic head and neck paraganglioma, diagnosed when she was 12 and relapsed after 10 years. She underwent anterior cervical corpectomy and C7 fusion with iliac bone graft, excision of right tracheal wall mass, and completion thyroidectomy. HPE: paraganglioma of the tracheal mass with metastasis to C7. MRI showed residual enhancing lesion at the larynx, thyroid beds, and paravertebral lesions C6-T1. She underwent radiotherapy to the neck region. FDG PET/CT showed FDG-avid disease at the right tracheal wall and right thyroid bed with nodal, lung, liver, and bone metastases. Ga68 DOTATATE PET/CT revealed somatostatin-avid disease in the thyroid bed with nodal, lung, liver, and bone metastases, concordant with FDG PET/CT. I-131 MIBG scintigraphy showed no evidence of MIBG-avid disease.

In the second case, a 34-year-old lady was diagnosed with right adrenal pheochromocytoma at the age of 15-years-old. She underwent a right adrenalectomy and remained asymptomatic for 10 years. However, she presented again with a history of cough and haemoptysis. CT Thorax showed mediastinal mass. A biopsy of the bronchus was consistent with paraganglioma. Ga68 DOTATATE PET/CT showed somatostatin receptor-avid disease in the mediastinal mass, right lower lobe, paravertebral soft tissue lesion at T12 vertebra level, right adrenal bed, and left femur. FDG PET/CT revealed FDG-avid disease in the mediastinal mass, right lung, and paravertebral lesion at T12 vertebra. I-131 MIBG scintigraphy showed MIBG-avid disease at the sub-carinal, right hilar, and right lower lobe.

Both patients had multiple surgeries of primary and metastatic tumours. Due to recent significant findings of recurrent and metastatic tumours proven biochemically and by conventional imaging, both patients underwent functional diagnostic imaging, i.e., FDG PET/CT, Ga68 DOTATATE PET/CT, and I-131 MIBG diagnostic scintigraphy, which showed metastatic disease. Both cases were discussed in a multidisciplinary tumour board (MDT) meeting to decide on definitive treatment. The choice of radionuclide therapy will be discussed based on avidity in functional imaging and consensus reached. Both patients in these two cases presented are eligible for the PRRT using Lu177 DOTATATE as a definitive treatment because the lesions predominantly showed higher avidity in Ga68 DOTATATE PET/CT compared to FDG PET/CT and I-131 MIBG diagnostic scintigraphy.

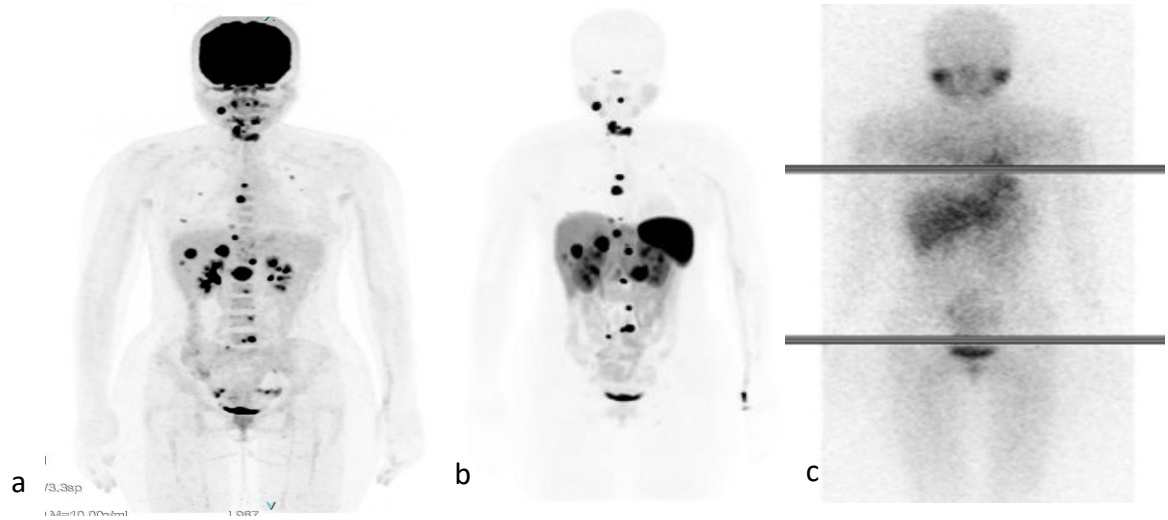

Fig. 1 FDG, Ga68 DOTATATE, and I-131 MIBG scintigraphy of a 23-year-old lady with metastatic paraganglioma. **a, b, c** The number of lesions demonstrated on maximum intensity projection (MIP) Ga68 DOTATATE images is higher than MIP FDG and I-131 MIBG. **B** The MIP of the Ga68 DOTATATE image shows multiple foci of somatostatin receptor-avid disease in a distribution consistent with metastases.

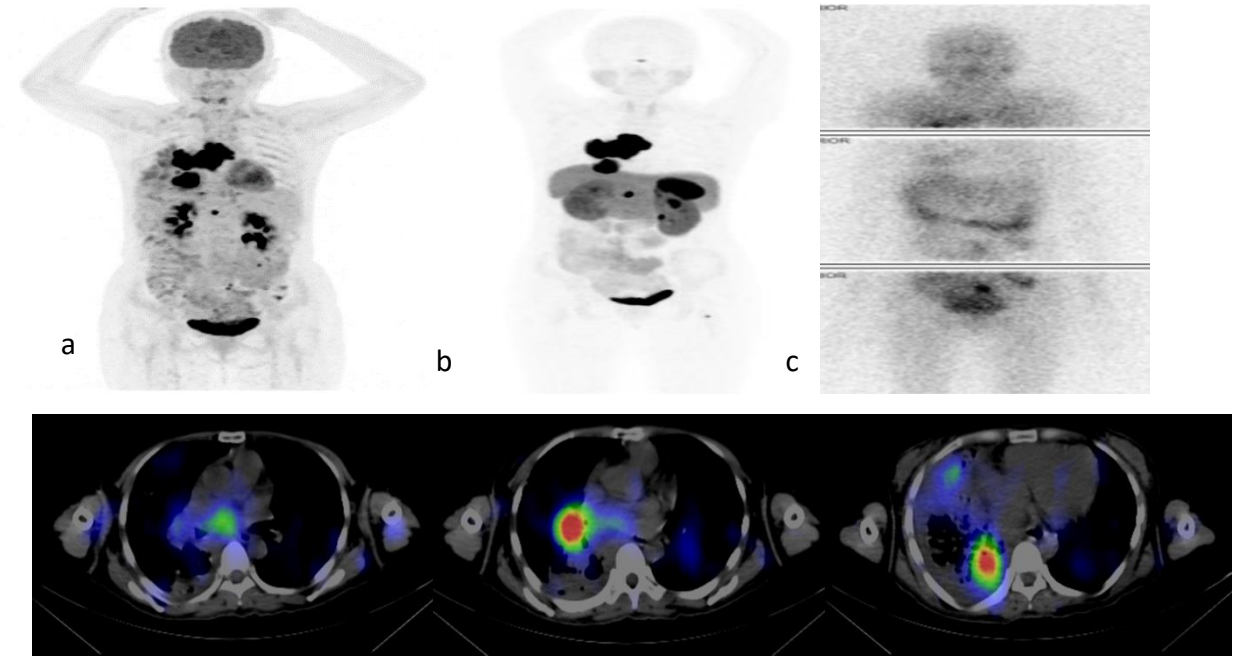

Fig. 2 FDG, Ga68 DOTATATE, and I-131 MIBG scintigraphy of a 34-year-old lady with metastatic paraganglioma. **a, b, c** The number of lesions demonstrated MIP Ga68 DOTATATE images outnumber MIP FDG images and planar I-131 MIBG images, Ga68 DOTATATE showed uptake in the left femur but FDG PET/CT and I-131 MIBG planar images showed no tracer uptake. **d** I-131 MIBG SPECT/CT images show MIBG-avid disease at the subcarinal, right hilar, and right lower lobe.

DISCUSSION:

Pheochromocytomas and paragangliomas (PPGLs) arise from chromaffin tissue of the adrenal medulla and extra-adrenal sympathetic/parasympathetic ganglia. Pheochromocytomas (PCCs) originate from the adrenal medulla, while paragangliomas (PGLs) arise from extra-adrenal paraganglia (Whitelaw et al., 2014). Choi (2020) stated that the incidence of PPGL was 2 to 8 per million per year. An epidemiology study by Kim et al. (2020) reported that PPGLs are rare in Korea, with a prevalence of 2.13 per 100,000 persons. Al Subhi et al. (2022) stated that due to incidental findings on imaging, the annual incidence of PPGL has increased over time. This is due to the advancement in anatomical and functional imaging modalities, such as CT scan, MRI, I-123/I-131 MIBG scintigraphy, FDG PET/CT, and the more recent Ga68 DOTATATE PET/CT. Nationwide epidemiological statistics on PPGLs are scarce in most countries, including Malaysia, and the prevalence might vary across populations.

Parasympathetic paraganglia are largely located in the head and neck and the anterior thoracic regions, with the commonest site in the carotid bodies. Meanwhile, sympathetic paraganglia are predominantly located in the abdomen, along the sympathetic chain in the prevertebral and paravertebral regions, adrenal medulla, urinary bladder, and the organ of Zuckerkandl. In other words, PPGLs can develop in any location in the body except in the bones (Asa et al., 2018).

The clinical appearances vary, influenced by catecholamine excess released by PPGLs. The classic triad of symptoms is headaches, palpitations, and profuse sweating. However, the symptoms are only seen in 25% of PPGL patients (Neumann et al., 2019). Commonly, most PPGL patients presented with worsening hypertension, such as persistent hypertension or paroxysmal hypertension. According to a recently published 2024 European Society of Cardiology (ESC) Guidelines for the management of elevated blood pressure and hypertension by McEvoy et al. (2024), PPGLS are an uncommon type of secondary hypertension with varied clinical symptoms. Other symptoms that may be present include pallor, nausea, vomiting, constipation, flushing, loss of weight, fever, orthostatic hypotension, chest and/or abdominal discomfort, hyperglycaemia, anxiety, and psychiatric findings. Depending on how much catecholamine excess there is, myocardial infarction, arrhythmia, and stroke may happen.

Different institutions may use different methods to diagnose patients. Some centres may have their own consensus on diagnosing PPGLs. Elevated levels of fractionated metanephrines and catecholamines in urine or plasma should biochemically confirm the diagnosis of PPGL. The most common investigation is 24-hour urine collection for fractionated metanephrines and catecholamines (Young, 2018).

Anatomical imaging, such as computed tomography (CT) and magnetic resonance imaging (MRI), are the first-choice imaging modalities to evaluate patients with PPGL. Anatomical imaging should only be done in patients with suspected PPGL once the diagnosis has been confirmed biochemically, with the exception of head and neck PGLs and other non-functional PPGLs due to unreliable biochemical tests (Timmers et al., 2024). The use of ultrasound is no longer advised due to its low sensitivity except for suspected PPGL in pregnant women and young children.

Advancement of functional imaging modalities over the last two decades has introduced single photon emission computed tomography (SPECT) and positron emission tomography (PET) for complementary imaging modalities for PPGLs. The role of these anatomical and functional imaging modalities, mainly for tumour localisation, is to assess locoregional recurrence and disease extension (Aygun, 2020). Currently, the introduction of integrated anatomical and functional imaging like hybrid SPECT/CT and PET/CT provides more accurate detail and superior diagnostic accuracy (Bockisch et al., 2009). Compared to SPECT, PET offers better image resolution besides less attenuation and scatter artefact, resulting in superior image quality and diagnostic capabilities. PET also has a wide range of radiotracers with higher sensitivity, making it excellent for clinical and research applications (Timmers et al., 2024).

Imaging with I-131 MIBG is a pioneer imaging modality for PPGL to locate primary tumours, locoregional recurrence, or metastatic diseases. This modality is based on the expression of cell membrane norepinephrine transporters (NET) and vesicular monoamine transporters (VMAT) present in these tumours (Rufini et al., 2013). I-131 MIBG diagnostic scintigraphy is recommended in patients to determine if they qualify for I-131 MIBG treatment. Patients who show adequate uptake and retention in PPGL lesions of I-131 MIBG diagnostic scintigraphy are eligible for I-131 MIBG therapy. A study by Timmers et al. (2009) confirmed that I-131 MIBG scintigraphy yielded high sensitivity for primary tumours and relatively poor (~50%) sensitivity for metastatic lesions. Similarly, Tan et al. (2015) observed that on a per-patient and per-lesion basis, I-131 diagnostic MIBG scintigraphy showed lower sensitivity in the detection of metastatic PPGL by 46.7% and 15.7%, respectively.

Studies have highlighted the overexpression of somatostatin receptors (SSTR) in PPGLs. Mundschenk et al. (2003) reported a 94% positive staining for somatostatin receptors in the study of 52 pheochromocytomas from 35 patients, which were stained with certain polyclonal anti-sst1–5 and monoclonal anti-SS-14 antibodies. Leijon et al. (2019) reported that SSTR2 and SSTR3 were most abundantly present in PPGLs. As these tumours express SSTRs, PET tracers like Cu64 DOTATATE and Ga68 DOTATATE are applied for PPGL lesion localisation, especially for SSTR type 2.

The European Association of Nuclear Medicine (EANM) has recommended Ga68 SSTR PET/CT for the detection, staging, and surveillance of PPGL because of the high SSTR expression in PPGL (Taïeb et al., 2019). Compared to I-131 MIBG scintigraphy, Ga68 SSTR PET/CT show

superior resolution, sensitivity, and specificity that are helpful in guiding the next step of management to localise the primary tumour or the extent of the disease. Singh et al. (2020) reported a significant association between the 24-hour urine metanephrine and free plasma metanephrine levels in I-131 MIBG scintigraphy and Ga68 DOTANOC PET/CT. Nevertheless, a higher number of patients showed tracer uptake in Ga68 DOTANOC PET/CT. Ga68 SSTR PET/CT can also be used for selecting patients for PRRT in an inoperable PPGL or metastatic disease not eligible for I-131 MIBG therapy due to inadequate or lack of I-131 MIBG diagnostic scintigraphy (Singh et al., 2020; Taïeb et al., 2019).

The role of FDG PET/CT in PPGL is mainly in lesions that have lost the SSTR expression and are commonly related to differentiated tumours, and these tumours alter their characteristics to more aggressive behaviour due to cellular de-differentiation. The shift from Ga68 SSTR avidity to FDG avidity is called the "flip-flop phenomenon" (Tan et al., 2015). FDG uptake in PPGL is not associated with catecholamine uptake in neurosecretory granules but is based on the accumulation of FDG in differentiated/malignant tumours via glucose transporter (Timmers et al., 2007). Patients with more FDG PET/CT uptake than Ga68 SSTR PET/CT or I-131 MIBG diagnostic scintigraphy are not suitable for radionuclide therapy. A meta-analysis by Kan et al. (2018) reported the pooled sensitivity and specificity of FDG PET/CT of 85% and 55% for metastatic pheochromocytoma and paraganglioma.

The patients were diagnosed with PPGL since childhood and underwent multiple surgeries for primary and metastatic tumours. However, the disease relapsed, and further biochemical assessments and conventional imaging revealed recurrent and extensive metastatic disease. The patients were referred to our centre for FDG PET/CT, Ga68 DOTATATE PET/CT, and I-131 MIBG diagnostic scintigraphy. The scans were performed to help decide on further conclusive intervention before the discussion in an MDT meeting. An MDT meeting is a compulsory practice in the centre to discuss surgical options and to select personalised targeted radionuclide therapy.

Functional imaging with FDG PET/CT, Ga68 DOTATATE PET/CT and I-131 MIBG diagnostic scintigraphy are complementary imaging modalities to evaluate the extent of the disease and to guide treatment strategy. Treatment strategies include surgery, systemic chemotherapy, radiotherapy and targeted radionuclide therapy. In our cases, Ga68 DOTATATE showed higher lesions uptake than FDG PET/CT and I-131 MIBG diagnostic scintigraphy, hence, both patients are eligible for PRRT as a definitive treatment mainly for symptomatic relief and tumour downstaging.

CONCLUSION:

In the light of theranostics approaches, multimodality radionuclide diagnostic imaging plays a pivotal role in completing disease staging and subsequent radionuclide therapy in PPGLs.

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