Case Report

MIBG THERAPY FOR LARGE RELAPSED PHEOCHROMOCYTOMA AND INOPERABLE PARAGANGLIOMA: CASE SERIES AND LITERATURE REVIEW

Reana Devi Arunasalem[1], Ahmad Zaid Zanial*[1]

[1]Nuclear Medicine Department, Hospital Kuala Lumpur, Ministry of Health Malaysia
Jalan Pahang, 50586 Kuala Lumpur, Malaysia.

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Corresponding author:
Dr. Ahmad Zaid Zanial

Email address:
ahmadzaidx@gmail.com

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ABSTRACT

Therapy using radioiodine labelled metaiodobenzylguanidine (MIBG) has been applied to treat advanced stage pheochromocytoma and paraganglioma that are not responding to standard treatment. Our centre has pioneered the MIBG diagnostic scan and therapy services beginning in 2013. We report two patients who received MIBG therapy for large relapsed pheochromocytoma and inoperable paraganglioma respectively to highlight the complexity of neuroendocrine neoplasia, contemporary role of this treatment modality as well as our initial experience. Investigations including MIBG diagnostic scan for both patients revealed huge primary lesion in the abdomen. They were referred to our centre for MIBG therapy. The first patient received it twice between 2015 and 2016, while the second patient had received it twice between 2018 and 2019. Their serial computed tomography (CT) scan and laboratory results have indicated some treatment response. Both patients have remained asymptomatic and demonstrated stable disease with no overt major therapy adverse effects observed during follow-up. MIBG therapy could potentially offer beneficial treatment response in selected patients with huge but single lesion as demonstrated in our patients with large relapsed pheochromocytoma and inoperable paraganglioma.

INTRODUCTION

Pheochromocytoma and paraganglioma (PPGL) are considered part of neuroendocrine neoplasia with a peak incidence between the third and fifth decades of life [1,2]. They are rare catecholamine secreting tumours derived from chromaffin cells originating in the neural crest namely adrenal medulla and extra-adrenal autonomic paraganglia respectively. Diagnosis of malignant disease is frequently made in retrospective manner when patients develop recurrent disease or metastatic presence of chromaffin tissues in extra-adrenal or extra-paraganglion sites [3-5]. Metastases are noted in 5%-20% of pheochromocytomas and 15%-35% of paragangliomas which tend to have poorer prognosis [6].

MIBG or iobenguane is an aralkyl guanidine and similar structurally to noradrenaline [7]. MIBG enters neuroendocrine cells by active uptake mechanism and stored in neurosecretory granules. Approximately 90% of chromaffin cell tumours concentrate MIBG which become the basis for functional imaging and therapy. MIBG can be labelled or tagged with radioiodine either Iodine-123 or Iodine-131, with the latter being available and widely used in our local clinical setting. When tagged with Iodine-131, the radiopharmaceutical can be used for therapy by taking advantage of the emitted beta radiation [8].

Our centre has pioneered the MIBG theranostic services in Ministry of Health, Malaysia since 2013. MIBG therapy requires admission to radioiodine ward and being offered mainly to adult patients, whereas MIBG diagnostic scans are done for paediatric and adult cases. Number of MIBG procedures have been increasing over the years. Hence, we report two patients who received MIBG therapies for large relapsed pheochromocytoma and inoperable paraganglioma to highlight the complexity of neuroendocrine neoplasia, contemporary role of this treatment modality and our initial experience.

CASE SERIES

Case 1: 56 years old male with history of hypertensive crisis and a huge right adrenal pheochromocytoma post-debulking surgery in 2013 had increasing

in size of residual tumour documented on follow-up. The lesion showed intense tracer uptake on MIBG diagnostic scan. He underwent chemoembolization in December 2014. Repeat CT scan revealed no significant change in tumour size (5.2 x 5.3 cm) despite larger central necrosis.

He then received MIBG therapy twice (15.4.2015 and 14.4.2016). Whole-body scan on day-5 post injection of the latest MIBG therapy revealed abnormal focus of MIBG-avid lesion at right upper paramedian of abdomen (Figure 1). Subsequent serial CT scans showed tumour size reduction (2.9 x 4.7 cm) and stable disease. Latest 24-hour urine metanephrine and normetanephrine were still raised but decreasing in trend from 9.89 umol/day and 12.92 µmol/day respectively in October 2015 to 4.98 µmol/day and 4.56 µmol/day in May 2018.

Case 2: 50 years old male presented with acute pulmonary oedema secondary to non-ST elevation myocardial infarction (NSTEMI) in 2017. Preliminary investigations revealed incidental findings of a big subhepatic paraganglioma. He underwent three sessions of transarterial tumour embolization. Initial MRI showed large heterogenous mass (7.8 x 7.4 cm) with splaying of adjacent structures, but serial CT scan showed only slight tumour size reduction. Collective surgical opinion concluded that resection will be high risk and challenging.

Functional imaging studies including MIBG diagnostic scan revealed concordant findings. He then received MIBG therapy twice (23.11.2018 and 26.9.2019). Whole-body scan on day-5 post injection of the latest MIBG therapy demonstrated a lobulated lesion with intense tracer accumulation in the upper abdomen (Figure 2). In relation to the therapy, his raised serum chromogranin A levels showed significant reduction from 2046 ng/mL in July 2018 to 879 ng/mL in May 2019.

Both patients were closely monitored previously during their admissions to our radioiodine ward (Figure 3). None reported any significant acute complications. They have also regularly attended follow-up clinic appointments after their therapy sessions whereby routine blood investigations such as full blood count, renal profile, liver function test and thyroid function test were reviewed. No overt major adverse therapy effects such as myelosuppression or haematological toxicity being observed in both patients. At present, they remained asymptomatic and demonstrated stable disease.

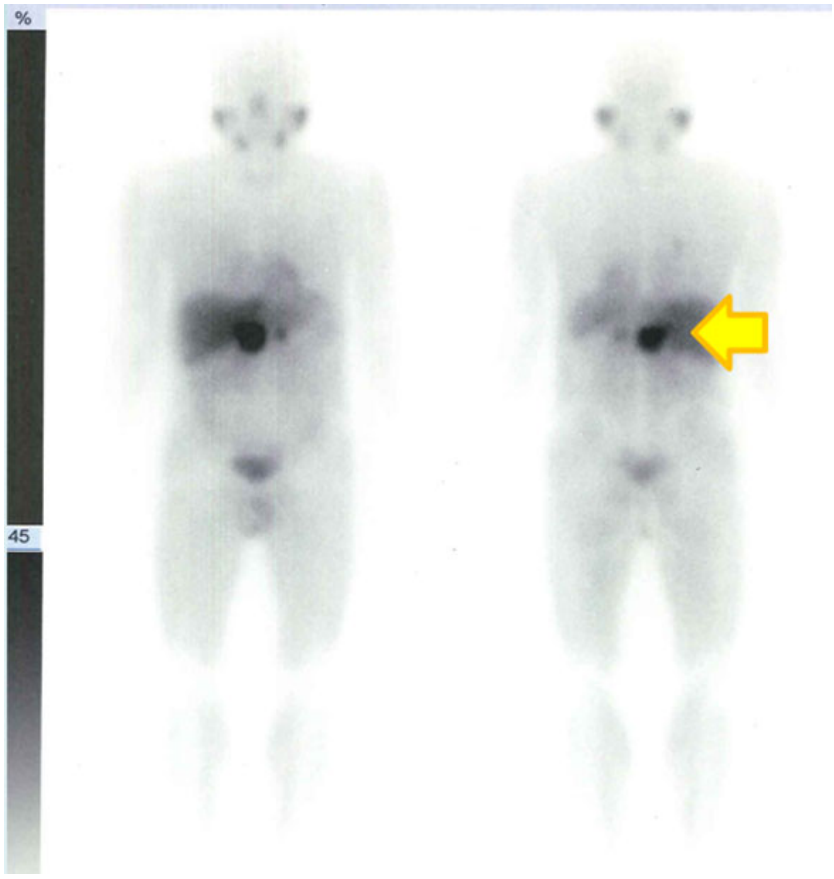

Figure 1: (Left-anterior and Right-posterior): Whole-body imaging on day-5 post MIBG therapy shows intense increased tracer uptake at the right upper paramedian of abdomen (yellow arrow) in keeping with clinical history of large relapsed pheochromocytoma.

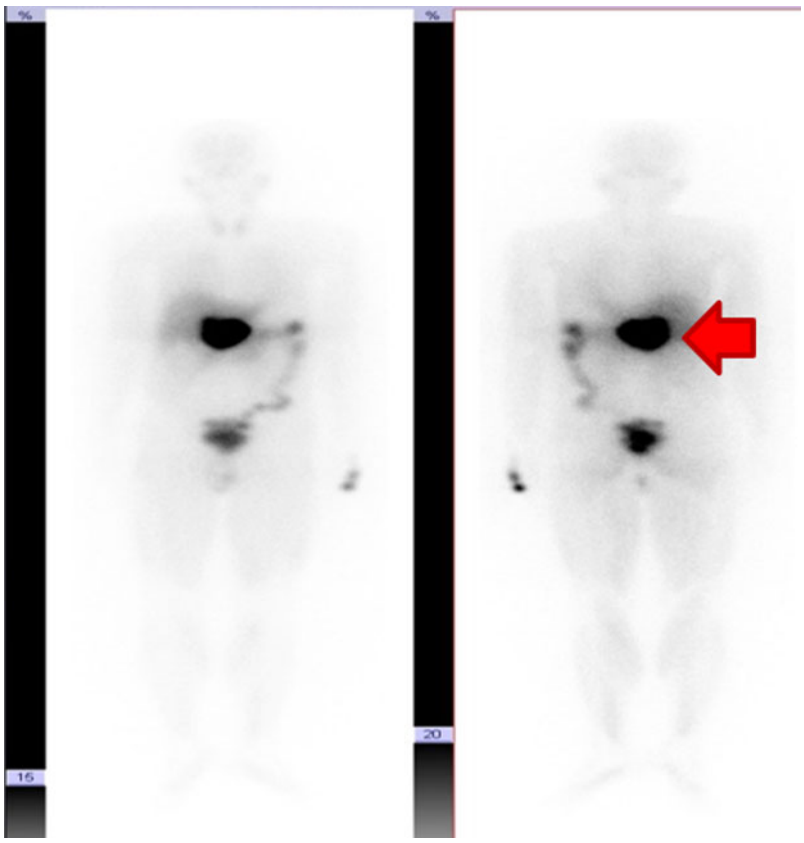

Figure 2: (Left-anterior and Right-posterior): Whole-body imaging on day-5 post MIBG therapy shows a lobulated lesion with intense increased tracer accumulation in the upper abdomen (red arrow) in keeping with clinical history of large inoperable paraganglioma

Figure 3: Radioiodine ward isolation room where MIBG therapy being administered. It is equipped with a lead-shielded trolley where the intravenous infusion pump being placed within.

DISCUSSION

Clinical presentation of the first patient was recurrent disease or relapse following debulking surgery. He also has history of hypertensive crisis. Whereas, the second patient had initially presented with NSTEMI. Investigations reveal large primary lesion in both patients. They underwent tumour embolization, but further assessment revealed no significant change in tumoral size. Each patient was referred to our centre and underwent MIBG therapy twice without any overt adverse effects noted. Their latest investigation results indicated some treatment response. Based on these two cases, we briefly discuss the challenges in managing PPGL and issues pertaining to MIBG therapy.

Some patients with PPGL may be asymptomatic, while others may present with wide array of presentations resulting from excess release of catecholamines or even complications from prolonged untreated exposure such as adverse cardiac event. Most signs and symptoms associated with hypercatecholaminaemia are non-specific [9]. However, hypertension is the most common finding associated with pheochromocytoma [10,11]. Apart from being a great mimicker, pheochromocytoma represents one of the most astounding medical puzzles where manifestations vary to barely understandable degrees in apparently comparable clinical settings [11].

PPGL are genetically diverse whereby genetic heterogeneity being observed between patients [6,12]. At least one-third of all patients with PPGL have disease-causing germline mutations and associated with certain syndromes or other tumours such as Von Hippel-Lindau and Multiple Endocrine Neoplasia type 2 [3,13]. Although most PPGL are benign, about 10%-15% are malignant for which there are limited therapeutic options [12]. Frequency of a malignant course also depends strongly on genetic background whereby mutations in gene for succinate dehydrogenase subunit B (SDHB) shown to be associated with high risk of malignancy [14].

Functional imaging with positron emission tomography (PET) using fluorodeoxyglucose (FDG) or Gallium-68 labelled somatostatin analogues is complementary in evaluating metastasis and guiding treatment [15]. Treatment include debulking surgery such as laparoscopic resection of primary lesion and surgical removal of metastases, targeted therapy, pharmacological control of hormone-mediated symptoms as well as systemic anti-neoplastic therapy [5,14,16]. In very advanced disease whereby surgical resection is not feasible, locoregional measures including embolization, radiofrequency ablation or selective internal radiation therapy can be used for tumour downstaging and achieving symptomatic relief [3].

On another note, monitoring of post-operative PPGL patients is essential because surgery might be incomplete, tumours might relapse, or metastases could develop even after several years [15]. Choi WS, et al. (2014) reported a case of malignant pheochromocytoma with local recurrence and metastases to the mediastinum and left lung approximately 11 years after a right adrenalectomy [10]. Furthermore, risk of recurrent disease is higher in young patients aged less than 20 years, those with syndromic presentations, paragangliomas and patients with large tumours [15].

Beside imaging studies such as CT scan, extended period of monitoring for post-surgery PPGL particularly high-risk patients should include yearly documentation of medical history, blood pressure checking and measurement of plasma or urinary fractionated metanephrines [15,17]. Levels of metanephrines provide more accurate measure for biochemical response because of strong relationship with tumour volume and being produced independently of variations in catecholamine release [14]. Additionally, plasma concentration of chromogranin A may provide an alternative marker of functional activity in PPGL patients [17].

Another treatment modality available for selected cases of high-risk PPGL particularly those who do not respond to standard treatment is MIBG therapy. Commonly accepted indications for MIBG therapy are inoperable PPGL and carcinoid tumour, malignant or metastatic PPGL, stage III or IV neuroblastoma and metastatic or recurrent medullary thyroid cancer [3,8]. In contrast, absolute contraindications include pregnancy, breastfeeding, life expectancy less than three months and renal insufficiency requiring short term dialysis [8].

Radioiodine labelled MIBG is selectively concentrated by neuroectodermal tissue and tumours rich in adrenergic innervation through similar process responsible for uptake and storage of catecholamines [7,14]. Eligible patients should demonstrate positive tumours on MIBG diagnostic scan in order to indicate that they may later benefit from administration of therapeutic Iodine-131 MIBG doses [8,18]. Once deposited within the tumour, mechanism of action for the radiopharmaceutical is by emission of beta radiation from the decaying Iodine-131 that will destroy adjacent tissues within mean range of about 0.5 mm [8].

Instruction and relevant information pertaining to preparation, procedure, complication and radiation protection should be conveyed to the patients. Patient preparations are important as many classes of medicines such as neurological, cardiovascular and sympathomimetic drugs could theoretically interfere with MIBG and thus may need to be withheld [7, 8]. Thyroid blockade using stable iodine for example potassium iodide and potassium perchlorate are advocated few days before and after MIBG therapy to prevent unwanted thyroidal uptake of free radioiodine causing hypothyroidism [8].

Locally, hospital admission to properly shielded isolation room with appropriate facilities and

radiation safety measures is required for MIBG therapy. The radiopharmaceutical is administered by slow intravenous infusion over period of 45 minutes to 4 hours using lead-shielded infusion system [8]. Patient monitoring particularly during and after the infusion is important as MIBG administration may result in unstable hypertension besides temporary nausea and vomiting. Other potential early adverse effects include thrombocytopenia and rarely renal function deterioration [8,14].

MIBG therapy can be given either in single or fractionated doses. Typical single-administered dosage is 100-300 mCi, but bone marrow has been well documented as the dose limiting organ [8]. A multicentre study involving 48 patients who underwent total of 87 treatment sessions of MIBG therapy with 100-400 mCi reported mostly minor side effects being observed in 41 treatment sessions [19]. Nevertheless, myelosuppression can occur as early or late side effect seen likely in patients with disease involvement in the marrow at the time of therapy and those with delayed renal clearance [8].

Even though some patients with limited disease and soft tissue rather than bone metastases could achieve partial or complete response and disease stabilisation, MIBG therapy in PPGL has generally been palliative [3,5,8]. Prior chemotherapy was noted to be a significant predictor of poor overall survival probably because those who received chemotherapy had large and rapidly progressive tumours [4,20]. Wakabayashi H, et al. (2013) reported a median survival of 56 months was observed among 26 malignant PPGL patients who underwent first MIBG therapy with 100-200 mCi [21].

There are several challenges in administering MIBG therapy particularly for higher treatment dosage beyond 200 mCi. In our setting, besides the costly imported radiopharmaceutical, radiation safety requirement and regulation by local authority on the permissible maximum administered therapeutic dosage need to be addressed. Although MIBG therapy with 500 mCi resulted in sustained blood pressure control and tumour response in PPGL, commonest treatment-emergent adverse events included myelosuppression [22]. Serious haematological toxicity due to high dose regimen can be circumvented if stem cell transplant support is available [8,20].

CONCLUSION

MIBG therapy could potentially offer beneficial treatment response as well as palliative role among selected PPGL patients with huge but single lesion as seen in our patients with relapsed pheochromocytoma and inoperable paraganglioma. They have demonstrated stable disease on follow-up with no overt major therapy side effects observed. Nevertheless, administration of MIBG therapy requires proper selection and preparation, thorough periprocedural observation and radiation safety measures as well as careful post treatment surveillance and disease follow up.

ETHICS

This report of case series has been registered with National Medical Research Register, Ministry of Health Malaysia (NMRR-20-707-54642) and received the permission from the Head of Nuclear Medicine Department, Hospital Kuala Lumpur. Efforts have been taken to ensure confidentiality of our patient. The authors declare no conflict of interests and did not receive any fund or grant for this case series publication.

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