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Case Presentation

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I-131 MIBG Treatment in Metastatic Malignant Pheochromocytoma

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Abstract

Pheochromocytoma is a rare neuroendocrine tumor originating from the chromaffin cells of the adrenal medulla and secretes catecholamines (metanephrine, normetanephrine). Approximately 95% of catecholamine-secreting tumors are located in the abdominal area; of these, 85 to 90% are intraadrenal (pheochromocytoma) and 5 to 10% are multiple or malignant pheochromocytomas. Malignant pheochromocytomas are histologically and biochemically identical to benign ones. A diagnosis of malignant pheochromocytoma is made by the presence of local invasion to surrounding tissues and organs or distant metastases that can appear even years after tumor resection. Individualized treatment approaches are required for patients with metastatic pheochromocytoma. There is no curative treatment for metastatic pheochromocytoma. For patients with metastatic disease secreting catecholamines and taking up MIBG, I-131 MIBG treatment is one of the therapies used for symptom relief and tumor regression or stabilization. In this case presentation, we share our experience of a 55-year-old male with a diagnosis of malignant pheochromocytoma, who progressed despite post-surgical lutetium treatment and achieved disease control with I-131 MIBG therapy.

Keywords: Malignant phaeochromocytoma; Treatment; Metaiodobenzylguanidine

Introduction

Pheochromocytoma is a rare neuroendocrine tumor that originates from the chromaffin cells of the adrenal medulla and secretes catecholamines. The annual incidence of pheochromocytoma is estimated to be about 0.8 per 100,000 individuals. Although it can occur at any age, it is most commonly seen in the fourth to fifth decades and occurs with equal frequency in men and women **[1-3].** Most cases are sporadic, while some are familial. There are various familial disorders associated with adrenal pheochromocytoma, all of which have autosomal dominant inheritance: von Hippel-Lindau (VHL) syndrome, Multiple Endocrine Neoplasia type 2 (MEN2), and Neurofibromatosis type 1 (NF1). The approximate frequency of pheochromocytoma in these disorders is 10 to 20% in VHL syndrome, 50% in MEN2, and 2 to 3% in NF1 **[4-6].** About 50% of patients with pheochromocytoma have symptoms, and when present, they are typically paroxysmal. The classic triad of symptoms in pheochromocytoma patients consists of episodic headaches, sweating, and tachycardia. About half have paroxysmal hypertension; most of the rest have either essential hypertension or normal blood pressure. Most patients with

pheochromocytoma do not have all three classic symptoms together, and patients with essential hypertension may have paroxysmal symptoms. Pheochromocytoma symptoms are caused by the tumoral excessive secretion of one or a combination of norepinephrine, epinephrine, and dopamine **[1].** In approximately 60% of patients, the tumor is incidentally discovered during abdominal Computed Tomography (CT) or Magnetic Resonance Imaging (MRI) for nonspecific symptoms **[7].** Malignant pheochromocytomas are histologically and biochemically identical to benign ones. A diagnosis of malignant pheochromocytoma is established by the presence of local invasion to adjacent tissues and organs or distant metastases that may emerge even years after tumor resection **[2].** The diagnosis of pheochromocytoma is established by the biochemical confirmation of excessive catecholamine secretion followed by imaging studies to identify the tumor. After biochemical confirmation of the diagnosis, radiological evaluation should be performed to determine the location of the tumor. Approximately 95% of catecholamine-secreting tumors are located in the abdominal area; 85 to 90% of these are intraadrenal (pheochromocytomas) and 5 to 10% are multiple or malignant pheochromocytomas **[1].** CT or MRI of the abdomen and pelvis is typically performed first. Since most have a diameter of 3 cm or larger, and both tests detect almost all sporadic symptomatic tumors, both are reasonable initial tests. If abdominal and pelvic CT or MRI are negative in the presence of clinical and biochemical evidence of pheochromocytoma, the diagnosis should be re-evaluated first. If the diagnosis is still considered likely, nuclear imaging studies such as Ga-68 DOTATATE PET, FDG-PET, or Metaiodobenzylguanidine [MIBG] I-123 scintigraphy may be performed. Whole-body nuclear imaging is unnecessary in patients with small sporadic solitary adrenal pheochromocytomas identified on CT/MRI. However, nuclear imaging is indicated in patients with large (>8 cm) adrenal pheochromocytomas or extra-adrenal masses due to the increased risk of multiple tumors and malignancy **[8].** An individualized treatment approach is required for patients with metastatic pheochromocytoma. There is no curative treatment for metastatic pheochromocytoma. Where possible, both primary and metastatic lesions should be resected **[9].** For patients with metastatic disease secreting catecholamines and taking up MIBG, I-131 MIBG treatment is one of the therapies used for symptom relief and tumor regression or stabilization. In this case presentation, we share our experience with a 55-year-old male diagnosed with malignant pheochromocytoma, who progressed despite post-surgical lutetium treatment and achieved complete biochemical and metabolic response with I-131 MIBG treatment.

Case Presentation

A 55-year-old male patient presented to an external emergency department with complaints of abdominal pain. Ultrasound and upper abdominal CT images revealed a 101013 cm mass lesion in the left suprarenal gland and a metastatic lesion in liver segments 5-6. Laboratory findings showed urine metanephrine levels >1840 nmol/L (normal range 44-261) and normetanephrine levels >12300 nmol/L (normal range 128-484). An F-18 FDG PET/CT was requested for identification of the possible primary malignant focus and determination of biopsy site. External F-18 FDG PET/CT images indicated that the mass lesion in the left suprarenal space, measuring 10914 cm, displayed heterogeneous increase in glucose metabolism and the SUVmax value was suggestive of malignancy. On 25.02.2019, the patient underwent left adrenalectomy, splenectomy, cholecystectomy, and liver metastasectomy. The diagnosis was reported as pheochromocytoma. Postoperative metanephrine: was 28 nmol/L and normetanephrine was 417 nmol/L. The resected left adrenal gland material exhibited high cellularity, necrosis, vascular/capsular invasion, confluent growth pattern, and nuclear pleomorphism with a KI-67 of 10%. The patient had postoperative GA-68 PET/CT at the external center, revealing numerous metastases in liver segment 3 and the skeletal system. Subsequently, the case was evaluated in a council meeting, and LU-177 DOTATATE therapy was planned. Following 2 cycles of LU-177 DOTATATE therapy, progression was observed in control GA-68 PET/CT, and the patient was reassessed with a council decision for I-131 MIBG therapy. He was referred to our center for MIBG therapy.

Initial I-123 MIBG whole-body imaging at our center **(Figure 1)** drew attention to increased I-123 MIBG uptakes in the left sphenoid bone, posterior right 6th costa, L4 vertebra, and right iliac bone (mild). Increased I-123 MIBG uptake in the hypodense lesion in liver segments 5-6 was noteworthy. In conclusion, the findings identified in the bones and liver were considered to be associated with metastases. The patient was treated with 200 mCi I-131 MIBG. The post-infusion image of I-131 MIBG is shown in **Figure 2**. Subsequently, he received 6 more I-131 MIBG treatments of 200 mCi each, accumulating a total dose of 1400 mCi. After 7 cycles of MIBG therapy, a complete metabolic response was achieved in all previous metastatic foci except for the lesion in the left sphenoid of the cranium. The lesion in the sphenoid bone was treated with 15 days of RT. Thereafter, sandostatin therapy was initiated for the patient.

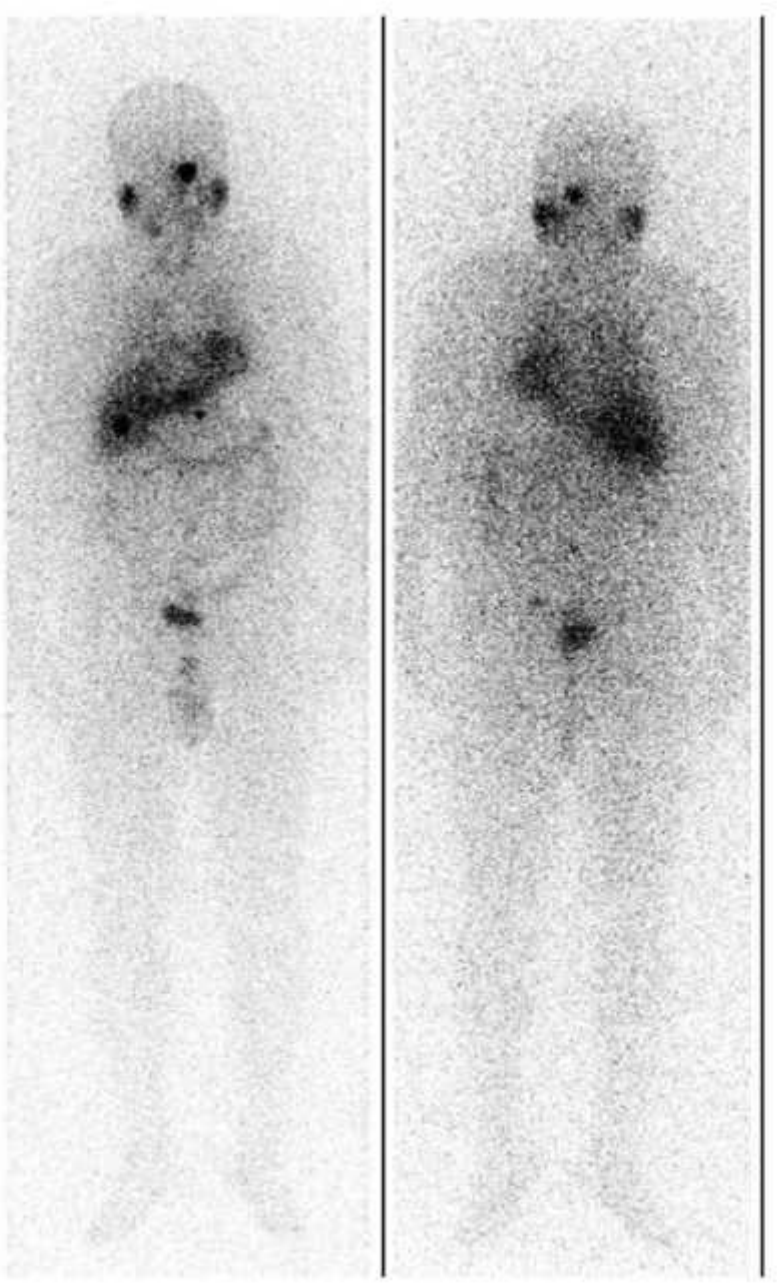

Figure 1: anterior and posterior I-123 MIBG diagnostic images.

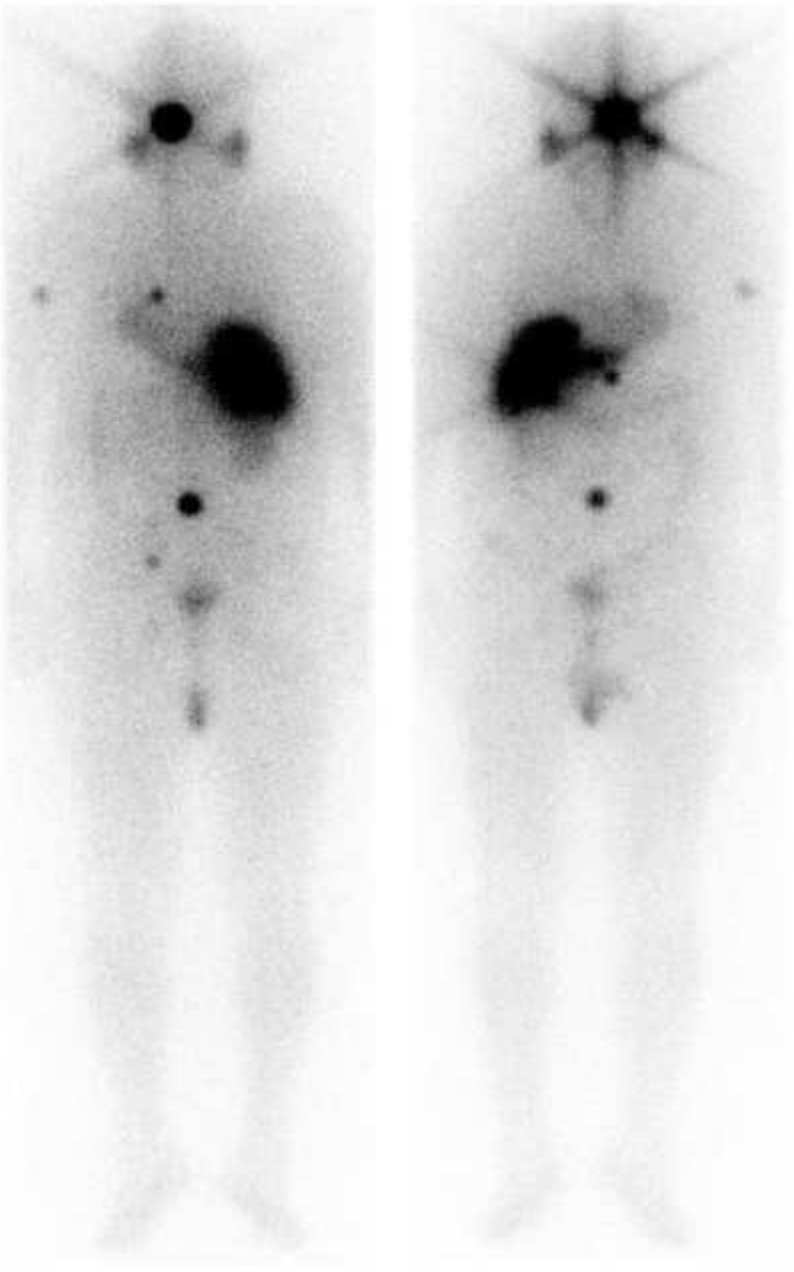

Figure 2: anterior and posterior I-131 MIBG images after first treatment.

In the whole body I-123 MIBG images **(Figure 3)** performed after all treatment; when evaluated in comparison with the I-123 MIBG study dated 06.08.2020; activity involvement defined in the left sphenoid bone, right 6th costa posterior, L4 vertebra, right iliac bone (mild) was not observed in this study and was thought to be related to response to treatment. I- 123 activity involvement defined in liver segment 2 was evaluated as similar.

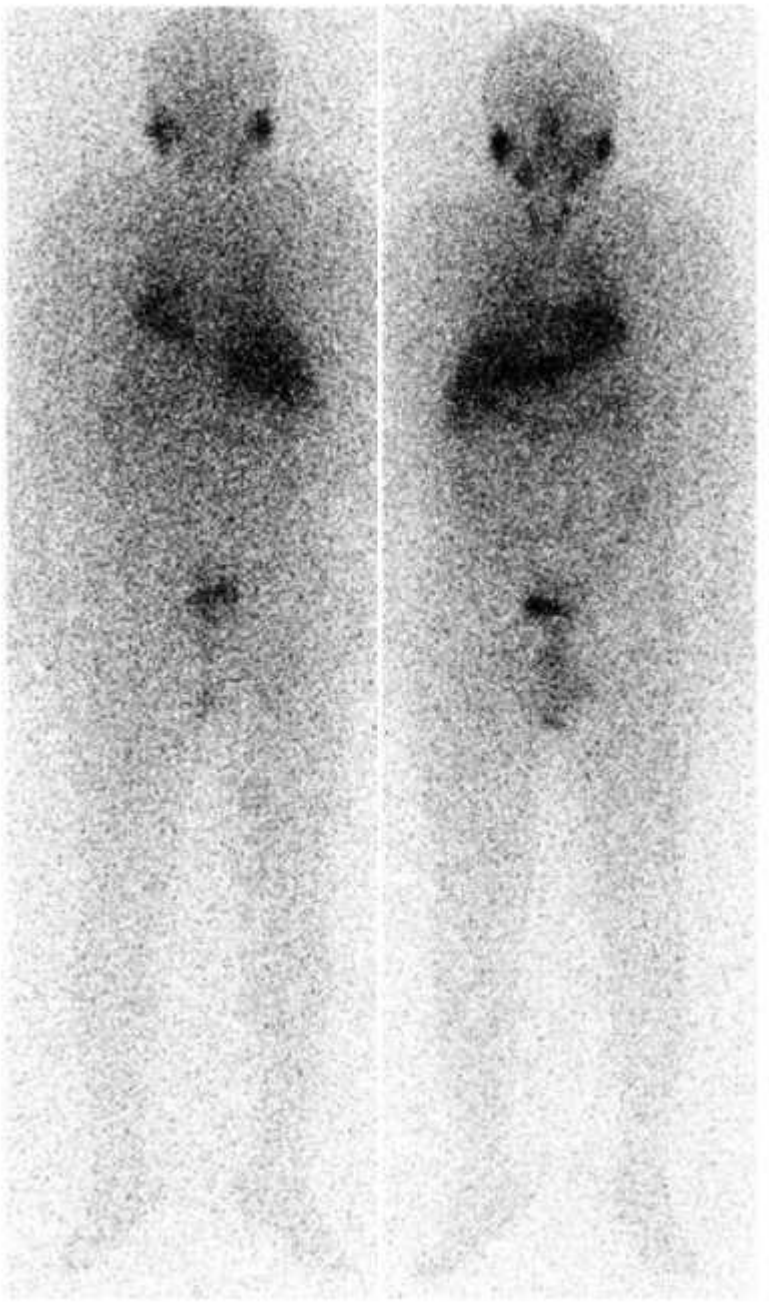

Figure 3: Anterior and posterior images in response to I-123 MIBG treatment.

Complete blood count, liver, kidney and thyroid function tests were normal before treatment. Although we performed thyroid prophylaxis with oral lugol for thyroid protection, hypothyroidism developed after the 4th cycle of I-131 MIBG treatment (TSH: 10 m(IU)/L). 50 mcg levothyroxine treatment was subsequently started. In subsequent follow-ups, euthyroidism was achieved. No other complications were observed in the patient after the treatments.

Discussion

The diagnostic and therapeutic value of MIBG is based on its structural similarity to norepinephrine and its high affinity and uptake by chromaffin cells. Radioactive iodine (I-131) is attached to the MIBG molecule to produce Iobenguane 131 (therapeutic). This treatment is effective in only about 60% of tumors that take up MIBG, as determined by Iobenguane I-

123 (diagnostic) scintigraphy **[10].** The therapeutic value of Iobenguane I-131 (therapeutic) in providing symptom relief and tumor regression or stabilization has been demonstrated in many case series for patients with metastatic disease secreting catecholamines and taking up MIBG **[10-13].** Objective response rates are approximately 30%, and the other 40% of tumors remain stable; less than 5% have a complete remission. A hormonal response (i.e., a decrease in catecholamine secretion) has been reported in 45 to 67% of cases **[10,12].** In our case, similar to these case series in the literature, complete metabolic, hormonal, and clinical responses were achieved after 7 cycles of treatment administered in 4-month periods, each with a cumulative dose of 1400 mCi. In the literature, Iobenguane I-131 (therapeutic) treatment is usually repeated at six-month intervals **[13].** We administered the treatment to our patient in more frequent intervals of four months. Optimal dosimetry has not been established in the case series in the literature. Most reports use single treatment doses of 100-200 mCi, with cumulative doses ranging from 557-2322 mCi and an average of 600 mCi **[11-14].** We administered 7 cycles of 200 mCi each to our patient, resulting in a cumulative dose of 1400 mCi of I-131 MIBI treatment. Treatment at the doses reported in the literature is generally well tolerated; the main side effects are transient mild leukopenia and thrombocytopenia. Hypothyroidism was reported in 3 out of 28 patients who received cumulative doses of 111-916 mCi in one series **[15].** Our patient also developed hypothyroidism, which was managed with replacement therapy to achieve euthyroidism.

In the literature, evidence suggests that higher-dose regimens (single doses of 500 to 800 mCi) may result in sustained complete responses in a small number of patients, although they carry a potentially higher risk of serious side effects **[16,17].** In a phase II study, 50 patients with metastatic pheochromocytoma/paraganglioma received single doses of Iobenguane I-131 (therapeutic) ranging from 492 to 1160 mCi (6 to 19 mCi/kg, median 12 mCi/kg); cumulative doses varied from 492 to 3191 mCi **[17].** Overall, a complete response was achieved in 10%, a partial response in 20%, and stable disease/minor response in 39% (69% disease control rate). The five-year overall survival rate was 64%. Toxicities included grade 3 to 4 neutropenia in 87% and grade 3 or 4 thrombocytopenia in 87%; prolonged myelosuppression requiring autologous hematopoietic cell rescue occurred in four patients. Other serious toxicities included grade 4 acute respiratory distress syndrome and cryptogenic organizing pneumonia in two patients, and myelodysplastic syndrome and concurrent acute leukemia in two patients receiving multiple Iobenguane I-131 (therapeutic) infusions. Despite the application of high doses of potassium iodide to prevent uptake of Iobenguane I-131 (therapeutic) by the thyroid and despite three patients being hyperthyroid, hypothyroidism was not reported **[17].** In our case, as the single dose administered was not as high as in this phase 2 study, we did not observe these side effects; however, we anticipate that due to the shorter intervals between treatments and the cumulative dose of treatment given being above average, we achieved complete metabolic, hormonal, and clinical responses, and we anticipate that our response duration will be longer than average. Given the fact that most studies use different doses and schedules of Iobenguane I-131 (therapeutic) and cover only a few patients, specific recommendations regarding the best dose and treatment plan cannot be made **[18].** Multicenter studies are needed to reach a consensus on the efficacy of high-dose versus fractionated moderate doses of Iobenguane I-131 (therapeutic) **[19].** In our case, we attempted to prevent the uptake of free iodide by the thyroid by orally administering saturated potassium iodide solution daily starting 48 hours before the planned application and for 5 days after the treatment; however, hypothyroidism still developed. Euthyroidism was achieved with replacement therapy. Patients should be counseled about the potential risks of prolonged myelosuppression and a possible increase in myelodysplasia and acute leukemia in long-term survivors **[20].** Although we did not escalate to such high doses, it is not clear whether these risks are limited to those receiving high-dose therapy. We informed our patient about these issues and closely monitored him with complete blood counts. As there is no common guideline for I-31 MIBG treatment, and because malignant pheochromocytoma is not yet curable, there is a need for numerous studies on this topic.

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