Indian Journal of Surgical Oncology (April 2021) 12 (Suppl 1):S186–S192
https://doi.org/10.1007/s13193-020-01259-4

CASE REPORT

Functional Malignant Retroperitoneal Paraganglioma with Liver Metastasis: a Rare Case Report

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Received: 26 June 2020 / Accepted: 24 November 2020 / Published online: 5 January 2021

Abstract

Paragangliomas are rare neoplasms. Their specific annual incidence is still unclear. These are rare neuroendocrine tumors which arise from extra-adrenal paraganglioma and they have the ability to secrete catecholamines. Most of them are diagnosed in the 3rd to 5th decades of life with mean age around 47 years. Majority of them are benign; however, malignant tumors with metastatic behavior are very rare. The incidence of malignant paraganglioma is estimated around 93/400 million people. The clinical course of metastatic malignant disease is variable and the reported 5-year survival is around 12–84%. There is no curative treatment option for malignant metastatic paraganglioma. If resectable, both, primary and metastasis should be resected. The only criteria which defines its malignancy is the presence of metastatic spread of chromaffin cells in tissues that normally do not contain such cells. Functional paraganglioma secretes excessive catecholamines which clinically manifest as paroxysmal hypertension, headache, sweating, and palpitations. We reported a case of young male who presented with huge left retroperitoneal mass and after evaluation found to have a functional malignant paraganglioma with liver metastasis. Surgical resection of the primary malignant paraganglioma with metastatectomy helps in decreasing the complications, improving the symptoms and prolonging the survival.

Keywords Paraganglioma · Functional · Metastatic · Catecholamine · Surgical resection

Introduction

Paragangliomas are rare neoplasms. Their specific annual incidence is still unclear. They are commonly described with pheochromocytomas as both are having similar clinical presentation and their combined annual incidence is around 0.8/100000 persons year [1] and in the USA, it is about 500–1600 cases per year [2]. These are rare neuroendocrine tumors which arise from extra-adrenal paraganglioma and they have the ability to secrete catecholamines. Most of them are diagnosed in the 3rd to 5th decades of life with mean age around 47 years [3]. Majority of them are benign; however, malignant tumors with metastatic behavior are very rare. The incidence of malignant paraganglioma is estimated around 93/400 million people [4]. Mostly, they are sporadic, but some syndromic association with hereditary diseases has been found like multiple endocrine neoplasia, neurofibromatosis and von Hippel-Lindau syndrome.

The clinical course of metastatic malignant disease is variable and the reported 5-year survival is around 12–84% [5]. There is no curative treatment option for malignant metastatic paraganglioma. If resectable, both, primary and metastasis should be resected [6]. The only criteria which defines its malignancy is the presence of metastatic spread of chromaffin cells in tissues that normally do not contain such cells [7]. Functional paraganglioma secretes excessive catecholamines which clinically manifest as paroxysmal hypertension,

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headache, sweating and palpitations [8]. We reported a case of a young male who presented with a huge left retroperitoneal mass with liver metastasis and after evaluation found to have metastatic paraganglioma.

Case Report

A 38-year-old gentleman with Eastern Cooperative Oncology Group (ECOG) Performance Status 1 with no comorbidity presented to our clinic with left side flank pain on and off for the last 2–3 months. The patient was evaluated at a local hospital with an ultrasound of abdomen considering it a renal colic and they found that there is a left retroperitoneal tumor possibility of arising from the left suprarenal gland, so the treating clinician advised for computed tomography (CT) of the thorax, abdomen, and pelvis. CT was suggestive of a large heterogeneous retroperitoneal tumor of size 15 × 13 cm with metastasis in the segments IV, V, and VI of the liver. He had been advised biopsy and biopsy was taken from the mass which was suggestive of paraganglioma. There was no other positive family history, medical history, treatment history or history of hospitalization for major illness in the past. There was no history of headache, palpitations and unexplained sudden sweating. On clinical examination, there was no remarkable finding on the abdomen and the rest of the systemic examination was unremarkable. His blood pressure readings were also within normal limits. Considering it a functional tumor, we asked for the 24-hour catecholamine and cortisol levels and we found that norepinephrine levels were significantly raised.

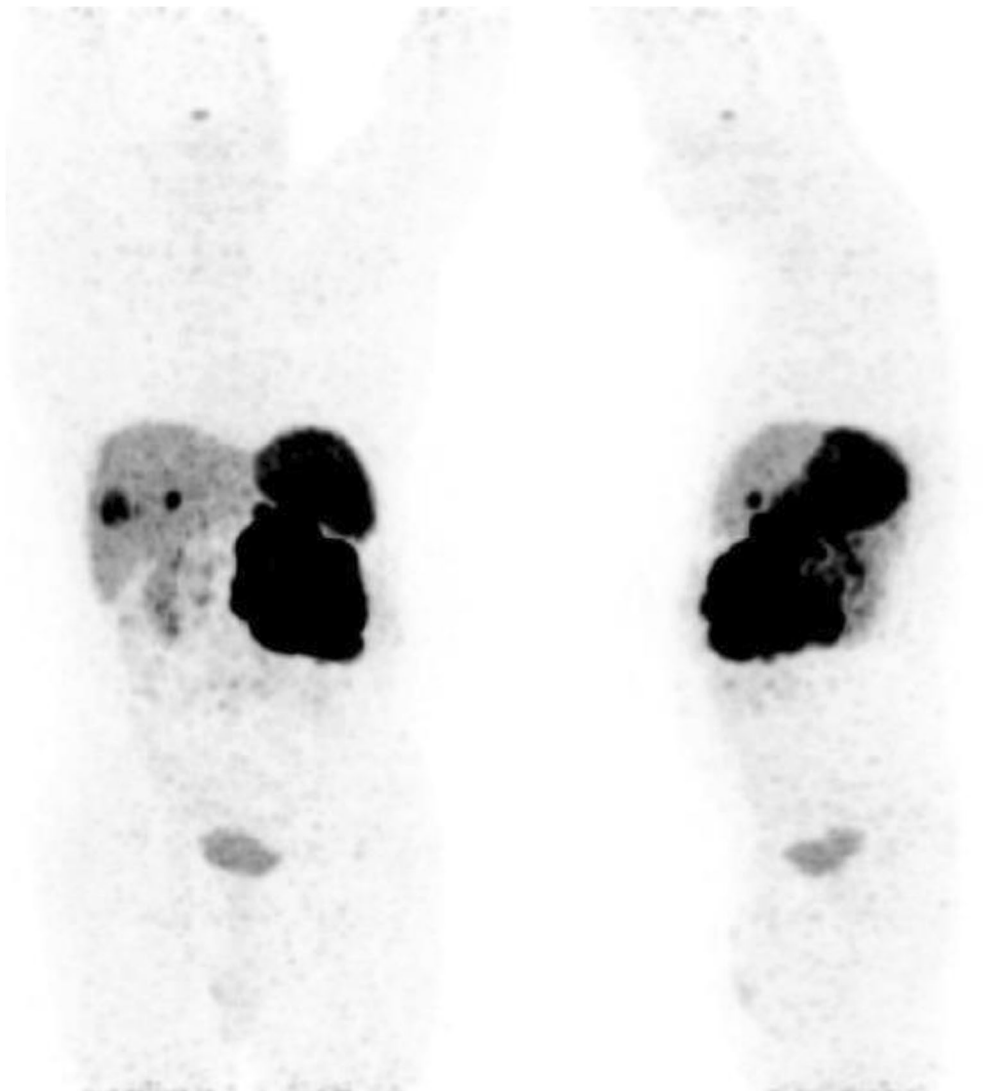

Fig. 1 Left retroperitoneal mass with liver lesion

Functional metastatic paraganglioma needs proper evaluation to know the accurate stage, so we asked for Ga 68-DOTANOC PET CT. This PET CT was suggestive of a large DOTANOC avid (SUV max. 16.7) heterogeneously enhancing lesion in the left supra renal and paraaortic regions with encasement of the left renal artery with extension across midline in the pre-aortic region (Figs. 1 and 2). The lesion had displaced the pancreatic body and tail anteriorly with measurement as (TRA) 12.8 × (AP) 14.9 × (CC) 14.4 cm in size with few mildly enlarged left paraaortic nodes (SUV max. 3.5), the largest one measuring 13 × 10 mm (Fig. 3). Another finding was that focal DOTANOC avid (SUV max. 19.7) enhancing lesions were seen in the segments IV, V, and VI of the liver, the largest one measuring 3.4 × 2.8 cm (Fig. 4). We were in dilemma with these findings and the next question was how to proceed further for this patient. Our multidisciplinary tumor board suggested multiple options of treatment like debulking surgery with metastatectomy, peptide receptor radioligand therapy, external beam radiation therapy, MIBG radionuclide therapy and molecular targeted therapy. Finally, the board decided to plan for a debulking surgery with metastatectomy as all liver metastases were resectable and advised a second opinion from the Tata Memorial Hospital, Mumbai. The second opinion was also in favor of our board's decision. We prepared the patient for this major surgery with an expert team of anesthetist and postoperative critical care monitoring unit. We operated him with midline laparotomy. Complete tumor debulking with retroperitoneal lymphadenectomy with metastatectomy of segments IV, V, and VI of the liver with adequate margins along with left nephrectomy was

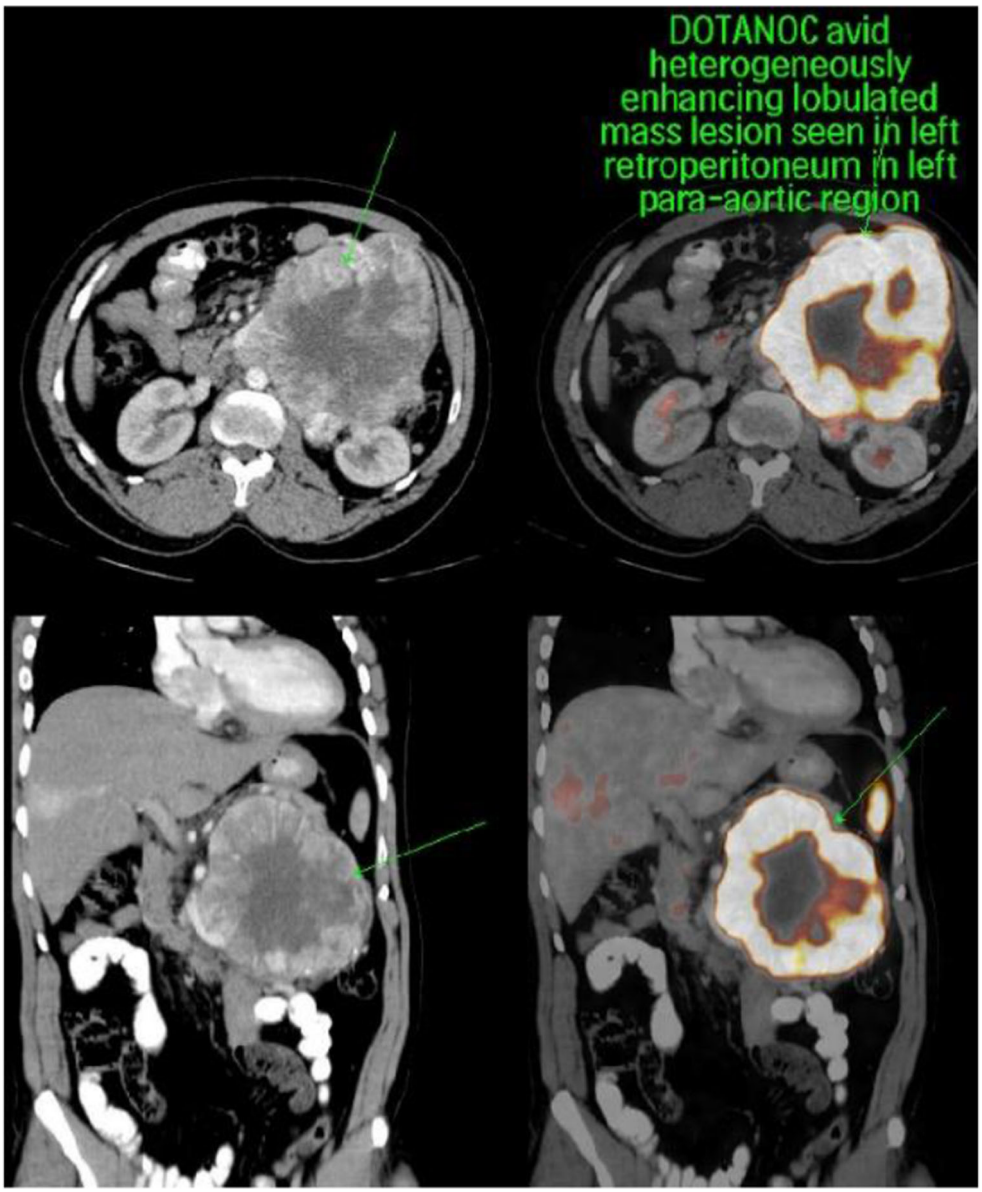

Fig. 2 Left retroperitoneal mass

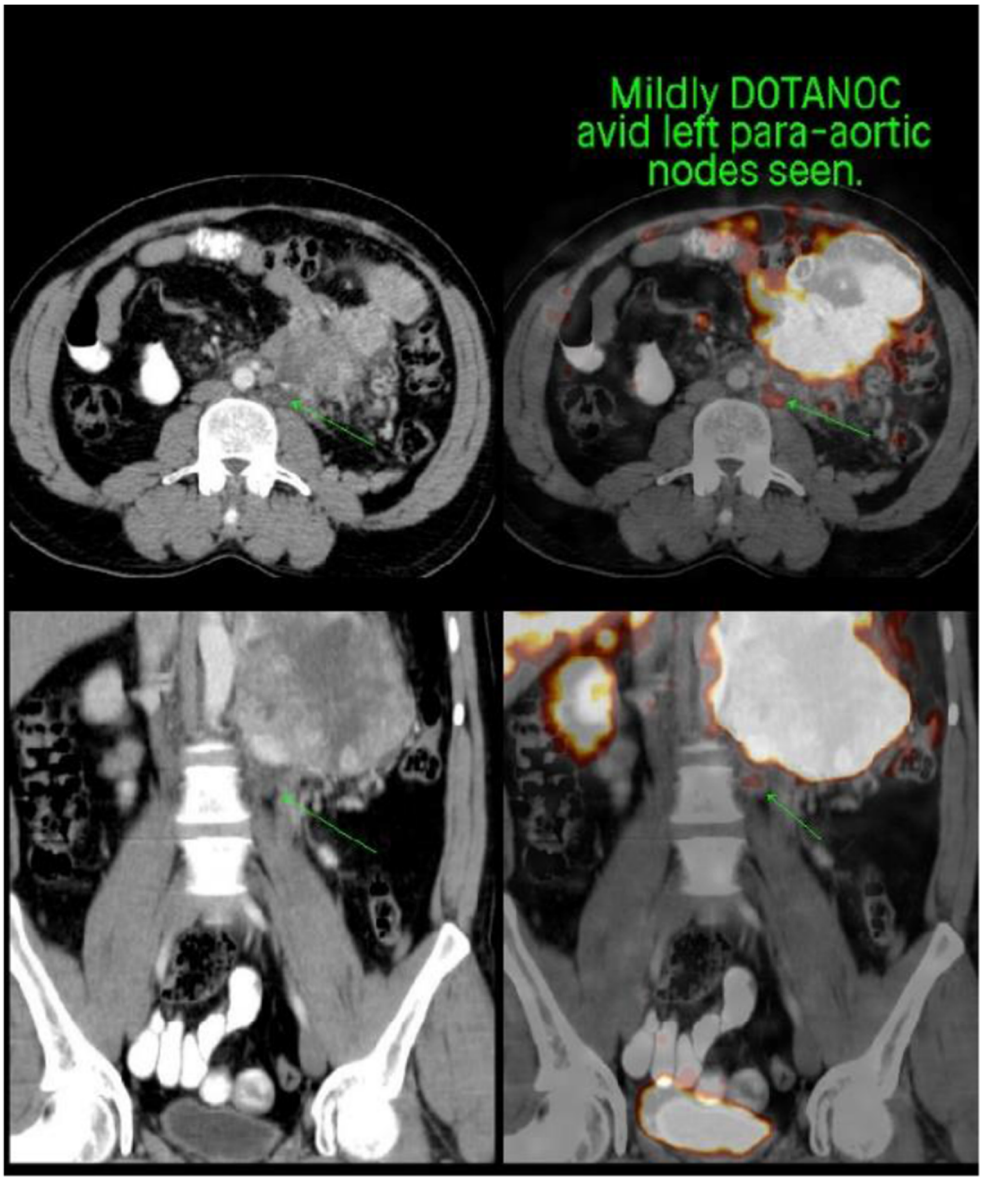

Fig. 3 Left paraaortic nodes

completed as there was a complete encasement of the left renal artery. It was a very vascular tumor, but the intraoperative period was uneventful. He was shifted to critical care room for 1 day and next day to the ward. The postoperative course was uneventful, and the patient was discharged on the 8th postoperative day. The final histopathology report was suggestive of paraganglioma with liver metastasis. Margins of metastatic specimens were clear and a total of 15 retroperitoneal lymph nodes were found which were free from malignancy. The patient had been advised adjuvant chemotherapy with cyclophosphamide, dacarbazine, vincristine and doxorubicin. But the patient and his relatives refused chemotherapy. Hence, we kept the patient on close periodic follow-up and after 2 years of completion of treatment, the patient is disease-free.

Discussion

Paraganglioma and pheochromocytomas usually share common clinical features at the cellular level and sometimes, pheochromocytomas are called intraadrenal paraganglioma [9]. The presentation of paraganglioma is similar as with pheochromocytoma and usually manifest as headache, palpitations, sweating, and tremors [10]. Sympathetic paraganglioma usually secretes catecholamines and they are located along the sympathetic paravertebral ganglia of the thorax, abdomen, and pelvis, while parasympathetic paraganglioma are usually non-functional and located along the glossopharyngeal and vagal nerves of neck and base of skull. Genetic testing is recommended for paraganglioma as some of the genes are responsible for its pathogenesis like

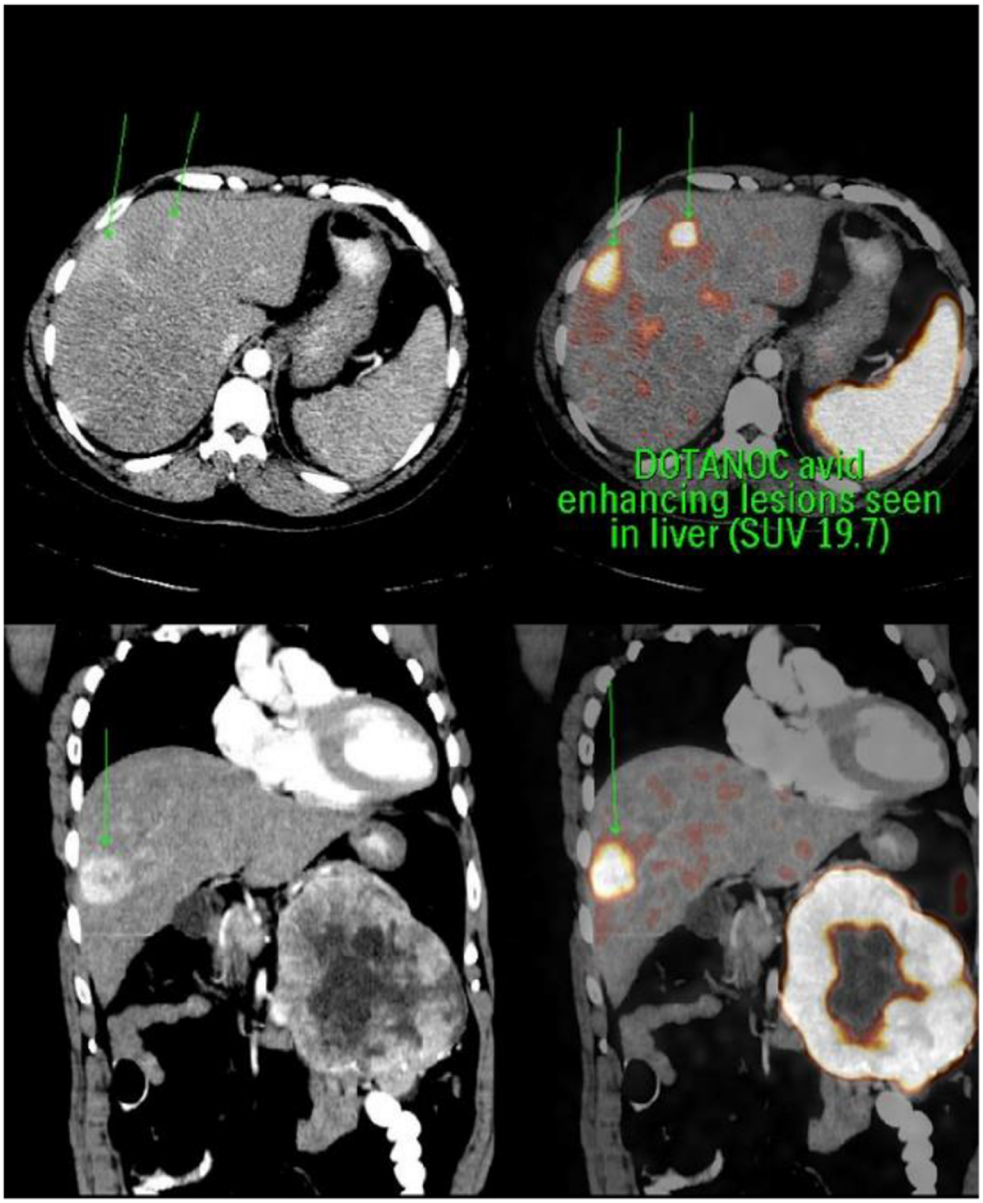

Fig. 4 Liver metastasis in segment IV,V & VI

mutations in the von Hippel-Lindau (VHL) tumor suppressor gene, the neurofibromatosis type 1 (NF1), tumor suppressor gene, genes encoding for the four subunits (A, B, C, D) of the succinate dehydrogenase (SDH) complex and the multiple endocrine neoplasia (MEN) gene.

The malignancy potential, clinical course and survival rates are different and variable for all types of paraganglioma. The factors affecting the prognosis of paraganglioma are the rate of progression of the disease, burden of the tumor and location of metastasis. Isolated bone metastasis has favorable prognosis in comparison to patients with the brain, liver and lung metastasis [11]. Paragangliomas manifesting with episodic hypertension, headache, palpitations and sweating should be evaluated for functional status and the diagnosis is confirmed by elevated catecholamine metabolites in plasma and/or raised 24-hour urinary excretion of fractionated metanephrines and catecholamines. Functional tumor with such clinical presentation should be initially managed with alpha and beta adrenergic blockers.

Various imaging options are available for staging workup. But functional imaging is considered superior than all other imaging. So positron emission tomography (PET) using the somatostatin receptor-based tracer gallium Ga-68 DOTATATE offers a better option for extra-adenal paragangliomas as compared to (18)F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and anatomical cross-sectional computed tomography Ga-68 DOTATATE is highly sensitive and can stage the advanced and metastatic disease with more accuracy [12].

If the primary disease and metastasis are resectable, then surgical resection is the best option. Resection improves the symptoms, reduces the complications caused by mechanical compression of tumor and makes the base ready for further treatment [13]. But the surgery should be in experienced hands with a team of expert anesthetist, skilled surgeon, and experienced intensivist. Until now, the survival benefit of surgical resection is unclear.

External beam radiation therapy (EBRT) was previously considered radioresistant for paraganglioma. But now, some of the case series have shown their benefits in local tumor control and symptomatic relief. However, it requires continuous monitoring because RT-induced inflammation of the lesion can induce massive catecholamine secretion and a hypertensive crisis [14]. The other non-surgical procedure for unresectable liver metastasis is transarterial chemoembolization (TACE). Some case reports had shown benefit in the reduction of tumor size and symptomatic improvement. However, it requires preprocedure medical preparation as there are chances of hypertensive crisis due to the massive release of catecholamines [15].

The other systemic therapy available is radionuclide therapy. MIBG has structural similarity with noradrenaline and it has high uptake and affinity in chromaffin cells. Radioactive iodine (I) is attached to the MIBG molecule to produce Iobenguane I-131 which produces its therapeutic effect on malignant paraganglioma. It is considered in cases with unresectable progressive disease with low number of bone metastasis and high tumor burden [16]. Another radionuclide therapy reported in a short case series is peptide receptor radioligand therapy. Most of the malignant metastatic paragangliomas express somatostatin receptors and it can be confirmed with PET CT with a Ga-68 DOTATATE scan. The most commonly used radionuclides are Yttrium-90-labeled DOTA-Tyr-octreotide (Y-edotreotide, Y-dotatoc) and lutetium Lu-177 DOTATATE (Lu-DOTATATE) [17, 18].

Octreotide has been used and reported by few case studies; however, their results are variable, so its use in malignant metastatic paraganglioma is still unclear. Systemic chemotherapy should be considered for malignant metastatic paraganglioma where the disease is fast progressing and unresectable with large number of bone metastasis and high burden of the tumor. Multiple studies are available with extensive data and the combination of chemotherapy regimens used includes cyclophosphamide, dacarbazine, vincristine, and doxorubicin [19]. The other treatment with molecular targeted therapy includes tyrosine kinase inhibitor, i.e., sunitinib. Until now, only in phase II randomized trials, efficacy of sunitinib has been proven [20]. Other targeted agents which are still in research are cabozantinib and everolimus.

Conclusion

Functional malignant metastatic paraganglioma is an extremely rare disease and it is a difficult challenge for treating clinicians to reach up to its diagnosis. Surgical resection of the primary malignant paraganglioma with metastatectomy helps in decreasing the complications, improving the symptoms, and prolonging the survival.

Data Availability Not applicable.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interests.

Ethics Approval and Consent to Participate Not applicable.

Statement of Informed Consent Informed consent was obtained from the patient for being included in the study.

Consent for Publication An informed consent to publish this case was obtained from the patient.

Clinical Trial Transparency Not applicable.

Guarantor of Submission The corresponding author is the guarantor of submission.

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