AACE Clinical Case Rep. 9 (2023) 149–152

Clinical Case Reports™
www.aaceclinicalcasereports.com

Case Report

Hypertensive Crisis in a Patient With a Functioning Mesenteric Paraganglioma: Dramatic Response to Octreotide Treatment

Omayma T. Elshafie, MBBS, MD [1,*], Abir C. Bou Khalil, MD [1], Maha A. Alshaibi, MD [2], Boris L. Itkin, MD, MSc [3], Babikir M. Ismail, MBBS, MD [4], Nicholas J. Woodhouse, OBE [1]

[1] Department of Endocrinology, Sultan Qaboos Comprehensive Cancer Care and Research Centre (SQCCCRC), Muscat, Sultanate of Oman
[2] Department of Surgery, Sultan Qaboos Comprehensive Cancer Care and Research Centre (SQCCCRC), Muscat, Sultanate of Oman
[3] Department of Medical Oncology, Sultan Qaboos Comprehensive Cancer Care and Research Centre (SQCCCRC), Muscat, Sultanate of Oman
[4] Department of Pathology, Sultan Qaboos Comprehensive Cancer Care and Research Centre (SQCCCRC), Muscat, Sultanate of Oman

ARTICLE INFO

Article history:
Received 22 November 2022
Received in revised form
26 April 2023
Accepted 3 May 2023
Available online 9 May 2023

Key words:
paraganglioma
octreotide
plasma catecholamines
68-Gallium DOTATATE PET/CT

ABSTRACT

Background/Objective: To report a dramatic and immediate clinical and biochemical response during treatment with octreotide in a patient with a functioning mesenteric paraganglioma (PGL).
Case Report: A 44-year-old woman was admitted with a severe hypertensive crisis and a blood pressure reaching 260/150 mm Hg. She was 2 months postpartum and had been previously diagnosed with pre-eclampsia. Secondary hypertension was suspected. This was confirmed by finding a 6 × 5-cm^2 retroperitoneal mass located using 68-Gallium DOTA–octreotate positron emission tomography/computed tomography and a grossly elevated plasma catecholamine level of 93 000 pmol/L (normal reference range: 650-2433 pmol/L). Treatment was immediately started with high doses of long- and short-acting octreotide. After 6 weeks and before surgery, the patient was normotensive, with a blood pressure of 120/70 mm Hg and a norepinephrine level of 6000 pmol/L. The tumor resection was uneventful, and histology confirmed the diagnosis. Following the surgery, the patient remained normotensive without any medications.
Discussion: PGLs and pheochromocytomas are neuroendocrine tumors, and most have receptors for octreotide. This case and another patient previously reported responded dramatically to treatment with a high dose of octreotide. Earlier reports of patients failing to respond are likely to have been the result of using a smaller octreotide dose.
Conclusion: We conclude that high doses of short- and long-acting octreotide are valuable in severely hypertensive patients. Our experience suggests that octreotide is of value in other patients with PGLs and pheochromocytomas. The response is rapid, sustained, effective, and with minimal reported side effects. To the best of our knowledge, this is the first report of a hypertensive crisis in a functional mesenteric PGL.

Introduction

Pheochromocytomas (PHEOs), located in the adrenal gland, and paragangliomas (PGLs), located in the extra-adrenal region, are rare neuroendocrine tumors that originate from adrenal medulla chromaffin cells or neural crest cells outside the adrenal gland.[1] They produce catecholamines and lead to classical clinical features in 40% of cases, which include episodic hypertension, headaches, diaphoresis, and flushing.[1] PGLs affect ~0.1% of individuals with hypertension.[1] The majority of PGLs are benign; however, a few of them are metastatic, leading to a decreased survival rate.[1] The majority of PGLs are sporadic; however, up to one third may be inherited and linked to germline mutations related to multiple endocrine neoplasia types 2A and 2B, neurofibromatosis type 1, von Hippel-Lindau, Carney triad, Carney-Stratakis dyad, and familial paraganglioma syndrome.[2] Mesenteric PGLs are rare, and

Abbreviations: BP, blood pressure; CgA, chromogranin A; CT, computed tomography; DOTATATE PET/CT, DOTA–octreotate positron emission tomography/computed tomography; PHEO, pheochromocytoma; PGL, paraganglioma; SA, short-acting.

* Address correspondence to Dr Omayma Taha Elshafie, Department of Endocrinology, Sultan Qaboos Comprehensive Cancer Care and Research Centre (SQCCCRC), P.O. Box 566 P.C:123, SQU Street Al Khoud, Muscat, Sultanate of Oman.
E-mail address: o.elshafie@cccrc.gov.om (O.T. Elshafie).

https://doi.org/10.1016/j.aace.2023.05.003

<15 cases have been reported in the literature since 2013.[2,3] The gold-standard imaging modality to detect PGLs has been I-123 metaiodobenzylguanidine; however, because PGLs are neuroendocrine tumors that express somatostatin receptors, 68-Gallium DOTA–octreotate positron emission tomography/computed tomography (DOTATATE PET/CT) should be considered as the ideal first-line investigation for PGLs and PHEOs because it has higher sensitivity in the detection of tumors than metaiodobenzylguanidine.[4,5] Pregnancies complicated by a PHEO or PGL occur in <1 of 1000 cases and result in a higher mortality rate when diagnosed after delivery.[6] In this article, we report a patient with a mesenteric catecholamine-secreting PGL diagnosed after delivery in whom high doses of short-acting (SA) and long-acting octreotide led to complete clinical and near-complete biochemical remission before successful surgical resection of the tumor.

Highlights

- This is a report of an extremely rare case of functioning mesenteric paraganglioma
- The 68-Gallium DOTA–octreotate positron emission tomography/computed tomography scan is of value in the localization of paragangliomas
- High doses of short- and long-acting octreotide may be of value in hypertension.
- Patient with pre-eclampsia should be screened for secondary causes of hypertension.

Clinical Relevance

Pheochromocytomas (PHEOs) and paragangliomas (PGLs) are rare neuroendocrine tumors and usually express receptors for somatostatin and, theoretically, should respond to treatment with octreotide. High doses of short- and long-acting octreotide may be of value in severely hypertensive patients. Our experience suggests that octreotide is of value in the treatment of symptomatic PGLs and PHEOs.

Case Report

A 44-year-old woman was admitted with a severe hypertensive crisis and a blood pressure (BP) reaching 260/150 mm Hg 2 months after undergoing a C-section for a presumed diagnosis of pre-eclampsia. She had been hypertensive for 7 years and diagnosed as having pre-eclampsia during her 4 pregnancies. When first seen, she had been taking 200-mg labetalol twice daily and 5-mg amlodipine daily. Outside abdominal computed tomography (CT) revealed a 6 × 5-cm^2 partially necrotic retroperitoneal mass (Fig. 1 *A*). A catecholamine-secreting PGL was suspected.

Investigations revealed severely elevated levels of plasma catecholamines, that is, norepinephrine (NE; 93 000 pmol/L [normal reference range: 650-2433 pmol/L]), with raised dopamine (2000 pmol/L [normal reference range: 475 pmol/L]) and chromogranin A (CgA) levels (450 pmol/L [normal reference range: <76 pmol/L]). Plasma and urine metanephrine levels are not available at our center. The 68-Gallium DOTATATE/DOTATOC PET/CT scan result was positive, confirming a metabolically active PGL with somatostatin receptors (Fig. 2). The patient had a normal echocardiography result, with a 65% ejection fraction.

The patient initially had severe headaches, sweating, tachycardia, and high BP, requiring admission to the intensive care unit for 10 days.

Because SA octreotide was not immediately available, treatment was, therefore, started with 40-mg long-acting octreotide administered intramuscularly every 2 weeks in view of a positive 68-Gallium DOTATATE PET/CT scan result. Two days after starting long-acting octreotide, SA octreotide at 200 μg administered subcutaneously every 8 hours for 1 week, which was dropped to 100 μg 8 hourly for another week, was added. On this regimen, there was a progressive fall in the NE and BP levels. The NE levels were collected on days 4, 7, 30, and 45. Ten days after starting treatment, the patient developed severe abdominal pain, and abdominal CT revealed further hemorrhage in the tumor (Fig. 1 *B*). The pain resolved spontaneously after 2 days. After 45 days and just before surgery, the NE level dropped to 6000 pmol/L (Fig. 3). α-Blockers were not available. Fortunately, our previous experience indicated that the use of octreotide was effective in patients with a positive 68-Gallium DOTATATE PET/CT scan result. Since admission, amlodipine was stopped and labetalol continued for 2 weeks and then discontinued.

The patient underwent successful surgical resection of the tumor, with no BP fluctuation during the procedure. Following the surgery, the patient became normotensive without taking any medications. Pathology showed a massively necrotic, mesenteric paraganglioma. The tumor cells were positive for chromogranin, synaptophysin, and CD56 (Fig. 4 *A* and *B*). The Ki67 expression was low at <1%.

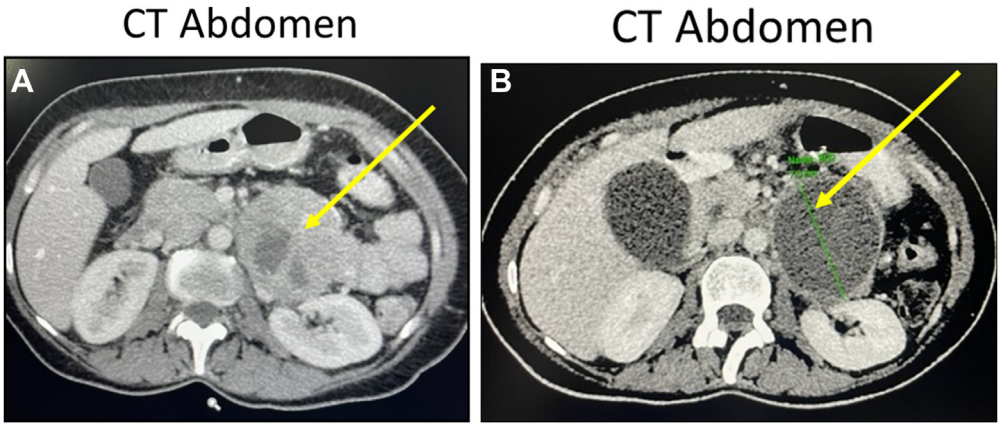

Fig. 1. Computed tomography of the abdomen. *A*, A left retroperitoneal mass measuring 6 × 5 cm^2. *B*, Increased necrosis in the left retroperitoneal mass that demonstrates a minimal increase in interval size. Yellow arrow is the normal reference range (650-2433) pmol/L. *CT* = computed tomography.

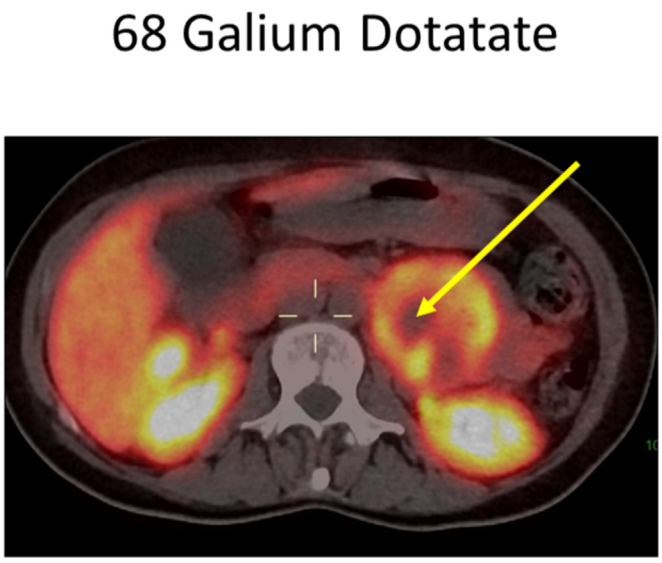

Fig. 2. A 68-Gallium DOTA–octreotate positron emission tomography/computed tomography whole-body scan showing a moderate somatostatin receptor–avid retroperitoneal mass, consistent with paraganglioma. *DOTATATE PET/CT* = DOTA–octreotate positron emission tomography/computed tomography.

Four months after surgical resection, the patient was clinically asymptomatic. Her BP was 120/65 mm Hg, and her heartbeat rate was 61 beats/min. Her plasma NE and CgA levels returned to normal without taking any medications. Genetic testing was performed, which showed no genetic mutations.

Discussion

PHEOs and PGLs are rare neuroendocrine tumors that usually express receptors for somatostatin and, theoretically, should respond to treatment with octreotide.[7] This was first clearly demonstrated in 2014, when a previous study reported a dramatic clinical and biochemical improvement in a patient with a carotid body PGL using high doses of octreotide.[8] Our present patient also responded favorably to a high dose of octreotide, with progressive reduction in NE, CgA, and BP levels. The dramatic biochemical improvement observed during therapy was mainly due to the effect of octreotide because her NE level fell from 93 000 to 15 000 pmol/L after the first 7 days of treatment and 3 days before the onset of her acute abdominal pain. The latter was due to further hemorrhage into her tumor, as can be seen in her CT scan. This might have resulted in some additional lowering of her NE level, observed after 6 weeks of treatment, at 6000 pmol/L just before the surgery.

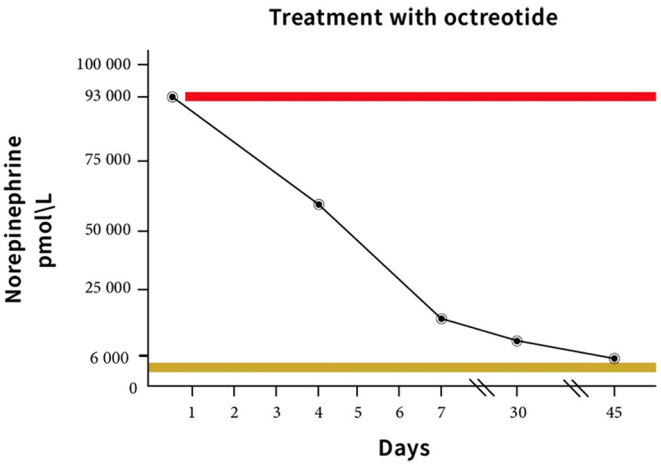

Fig. 3. Serum norepinephrine levels before and during treatment with octreotide.

In both of these patients, surgery was curative and uncomplicated. Our current patient's presenting history is also interesting. She had been diagnosed with pre-eclampsia in her 3 previous pregnancies and was admitted here with severe hypertension taking 200-mg labetalol twice daily 2 months after a C-section during her fourth pregnancy. This is most unusual in patients with pre-eclampsia whose BP usually returns to normal a few weeks after the placenta is removed. This clinical observation and the finding of a partially necrotic retroperitoneal tumor on a CT scan obtained outside indicated a secondary cause for her elevated BP. A metabolically active PGL was confirmed after finding high NE and CgA levels as well as a positive 68-Gallium DOTATATE PET/CT scan result. The relatively low epinephrine level suggests a nonadrenal site of catecholamine production.

Pre-eclampsia is quite common and, in many ways, behaves like a neuroendocrine tumor. Patients are hypertensive, placental CgA expression is increased, and high BP resolves after removal of the placenta.[9] Patients whose BP is not controlled after placental removal, as in our patient, should have a secondary cause excluded.

Two other patients who had metastatic PGLs were also treated with octreotide: 1 using high doses, which were very effective,[10] and the other with low doses, which had no effect on catecholamine levels.[11] Three reported articles have indicated a lack of response to octreotide. This may be attributed to the use of small doses of octreotide for a short duration, $\leq$24 hours.[12-14] The dosage requirement for octreotide can be assessed using a therapeutic trial, as indicated in our article. Our current practice is to administer a therapeutic trial dose of 200-μg SA octreotide 8 hourly subcutaneously for 1 week, with serial BP and catecholamine measurements. This will identify patients who are likely to respond to long-acting octreotide treatment and the required dosage.

Most previously reported cases of mesenteric PGL were either detected incidentally or due to abdominal pain; however, none of them had clinical symptoms of excess catecholamine.[2,15] On the other hand, our patient had full-blown symptoms and presented with a hypertensive crisis.

Conclusion

We conclude that high doses of SA and long-acting octreotide may be of value in severely hypertensive patients. Our experience suggests that octreotide is of value in the treatment of symptomatic PGLs and PHEOs. The response is rapid, sustained, effective, and with minimal side effects. Patients diagnosed as having pre-eclampsia should be carefully screened for secondary causes of hypertension if their BP does not return to normal a few weeks after placental removal. To the best of our knowledge, this is the first report of a hypertensive crisis in a functional mesenteric PGL.

Disclosure

The authors have no multiplicity of interest to disclose.

Acknowledgment

Informed consent has been obtained from the patient.

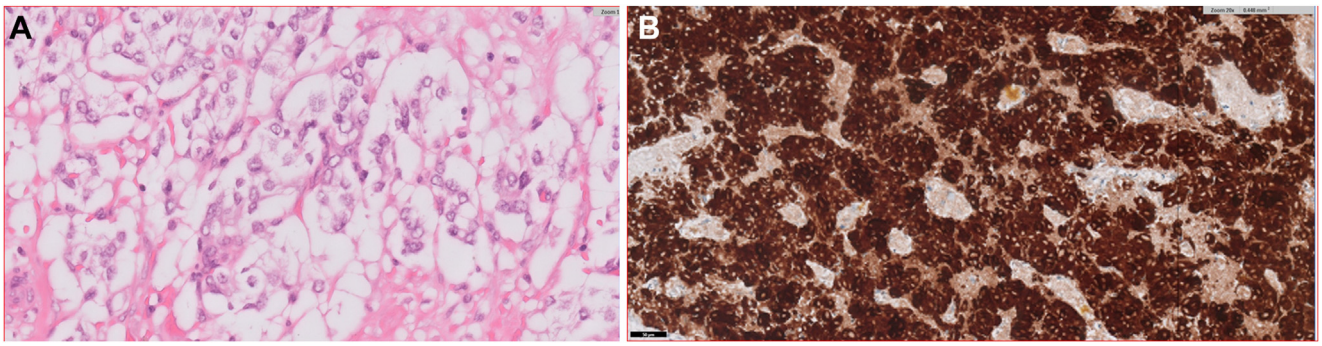

Fig. 4. *A*, Hematoxylin and eosin staining at ×40 magnification showing a "zellballen" pattern. *B*, Immunohistochemical evaluation positive for chromogranin A.

References

1. Cerqueira A, Seco T, Costa A, Tavares M, Cotter J. Pheochromocytoma and paraganglioma: a review of diagnosis, management and treatment of rare causes of hypertension. *Cureus*. 2020;12(5):1–6.
2. Rocco R, Murphy B, Patel V, Hamidi O, Chang A, Lyden M. A rare case of a 65 year old female with a mesenteric paraganglioma. *Human Pathol Case Rep*. 2020;19, 200349.
3. Chetrit M, Dubé P, Royal V, Leblanc G, Sideris L. Malignant paraganglioma of the mesentery: a case report and review of literature. *World J Surg Oncol*. 2012;10(1):1–6.
4. Chang CA, Pattison DA, Tothill RW, et al. 68Ga-DOTATATE and 18F-FDG PET/CT in paraganglioma and pheochromocytoma: utility, patterns and heterogeneity. *Cancer Imaging*. 2016;16(1):1–12.
5. Taïeb D, Hicks R, Hindié E, et al. European Association of Nuclear Medicine Practice Guideline/Society of Nuclear Medicine and Molecular Imaging Procedure Standard 2019 for radionuclide imaging of phaeochromocytoma and paraganglioma. *Eur J Nucl Med Mol Imaging*. 2019;46(10):2112–2137.
6. Wing LA, Conaglen JV, Meyer-Rochow GY, Elston MS. Paraganglioma in pregnancy: a case series and review of the literature. *J Clin Endocrinol Metab*. 2015;100(8):3202–3209.
7. Patel M, Tena I, Jha A, Taieb D, Pacak K. Somatostatin receptors and analogs in pheochromocytoma and paraganglioma: old players in a new precision medicine world. *Front Endocrinol*. 2021;12, 625312.
8. Elshafie O, Al Badaai Y, Alwahaibi K, et al. Catecholamine-secreting carotid body paraganglioma: successful preoperative control of hypertension and clinical symptoms using high-dose long-acting octreotide. *Endocrinol Diabetes Metab Case Rep*. 2014;2014(1):1–4.
9. Bralewska M, Biesiada L, Grzesiak M, et al. Chromogranin A demonstrates higher expression in preeclamptic placentas than in normal pregnancy. *BMC Pregnancy Childbirth*. 2021;21(1):1–10.
10. Brancíkova D, Mechl Z, Adam Z, et al. Patient with inoperable pheochromocytoma. *Curr Oncol*. 2015;22(3):216–219.
11. Jha A, De Luna K, Balili CA, et al. Clinical, diagnostic, and treatment characteristics of *SDHA*-related metastatic pheochromocytoma and paraganglioma. *Front Oncol*. 2019;9:1–17.
12. Lamarre-Cliche M, Gimenez-Roqueplo AP, Billaud E, Baudin E, Luton JP, Plouin PF. Effects of slow-release octreotide on urinary metanephrine excretion and plasma chromogranin A and catecholamine levels in patients with malignant or recurrent phaeochromocytoma. *Clin Endocrinol*. 2002;57(5):629–634.
13. Invitti C, De Martin I, Bolla GB, et al. Effect of octreotide on catecholamine plasma levels in patients with chromaffin cell tumors. *Horm Res*. 1993;40(4):156–160.
14. Plouin PF, Bertherat J, Chatellier G, et al. Short-term effects of octreotide on blood pressure and plasma catecholamines and neuropeptide Y levels in patients with phaeochromocytoma: a placebo-controlled trial. *Clin Endocrinol*. 1995;42(3):289–294.
15. Granger J, Mahapatra R, Hamid B, Gillespie K, Fok M, Vimalachandran D. Incidental mesenteric paraganglioma: a case report and literature review. *Ann Coloproctol*. 2017;33(5):197–200.