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Caso Clínico

Surgical Cytoreduction Against Malignant Pheochromocytoma: Case Report

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A B S T R A C T

Pheochromocytoma is a rare pathology, even more so its malignant presentation. It is an aggressive entity but with an acceptable survival, liable to palliative treatment with good results. Currently available therapeutic options are surgical debulking, radiopharmaceutical therapy (IMIBG Y and Lu-DOTATATE), chemotherapy and targeted therapy. The timing at which metastatic patients benefit most from systemic therapy has not yet been established. However, at some point they will require resective surgical treatment.
Expectant management is accepted whenever is possible. When the symptomatology is flowery and difficult to manage medically, the therapeutic range is imposed being the treatment option a combination between surgical reduction and 131I-MIBG.

Palavras-chave:
Compostos Radiofarmacêuticos/uso terapêutico;
Feocromocitoma/tratamento;
Procedimentos Cirúrgicos de Citorredução.

Citorredução Cirúrgica Contra Feocromocitoma Maligno: Relato de Caso

R E S U M O

O feocromocitoma é uma patologia rara, ainda mais sua manifestação maligna. É uma entidade agressiva mas com uma sobrevida aceitável, sujeita a tratamento paliativo com bons resultados.
As opções terapêuticas atualmente disponíveis são a citorredução cirúrgica, terapia radiofarmacêutica (I-MIBG Y e Lu-DOTATATE), quimioterapia e terapia direcionada. O momento em que os pacientes metastáticos mais se beneficiam da terapia sistêmica ainda não foi estabelecido. No entanto, é claro que em algum momento eles necessitarão de tratamento cirúrgico ressectivo.
Tratamentos expectantes são aceitos sempre que possível. Quando a sintomatologia é rebuscada e de difícil manejo médico, o leque terapêutico é definido de modo a escolher a combinação de redução cirúrgica e 131IMIBG.

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Introduction

Catecholamine-producing tumors originating from chromaffin cells of adrenal topography are known under the name of pheochromocytomas, a rare entity that can manifest itself in the context of other familial hereditary syndromes (25%).[1]

Those that occur in extra-adrenal tissue are called paragangliomas, being important the distinction between the two. The highest incidence is between the fourth and fifth decades of life, without gender predominance. These are usually asymptomatic tumors and their finding is incidental (incidentaloma).[2]

The classic symptomatic presentation is the well-known triad consisting of headache (80%), palpitations (64%) and diaphoresis (57%),[3] a, which depends on the production of catecholamines. Diagnostic confirmation is performed by measuring catecholamines, plasmatic and in 24-hour urine metanephrines.

Tumor localization requires imaging study. Computed tomography shows the lesion as unique, heterogeneous, oval, with a coefficient of attenuation without contrast greater than 10 Hounsfield units (HU).[4]

Magnetic resonance imaging is mainly used in children or pregnant women, being characteristic the unique hyperintense image in T2.

Those classified as malignant, are defined as such with distant metastases at the time of diagnosis or years later in evolution. It is estimated that 10%-20% of pheochromocytomas are malignant.[5] These patients should be studied using functional imaging methods such as scintigraphy and positron emission tomography.

The scintigraphy is performed with isotopes 123IMIBG or 131I-MIBG, the former being preferable due to its shorter half-life and greater sensitivity (83%). The use of both isotopes increases sensitivity to 100%.6

In some cases, inconclusive for metastasis, maybe necessary to perform a PET scan with 18F-FDG or 18F-FDA. Therefore, several studies propose higher performance of PET with 18F-FDA compared to 123I-MIBG for the assessment of metastatic disease.[7]

Treatment is essentially surgical for either pheochromocytoma or metastatic lesions and involves complete resection of the lesion.

Case Report

Male, 57 years old with a history of pheocromocitoma operated 8 years ago. During control assessment, patient begins with high blood pressure. Catecholamines, metanephrines and vanilmandelic acid were requested. It stands out from these: elevated metanephrines and ac vanilmandelic of 18.2 mg /24 hours (normal less than 8 mg/24 hours).

Assessment is completed with magnetic resonance imaging (MRI) that shows three solid lesions of 19, 5 and 7 mm in the hepatic segment 7 hypointense in T1, intermediate in T2; and multiple solid peritoneal nodules (hypointensum in T1, intermediate in T2, of variable size between subcentimeters to 30 mm nodule).

Endoscopic studies (fibrogastroduodenoscopy and colonoscopy) did not show any alterations.

The evaluation was complemented with PET 18F-FDG showing peritoneal nodules without catchment. PET Ga-DOTATATE revealed multiple lesions compatible with peritoneal implants with great avidity for radiotrace and therefore express somatostatin receptors.

Genetic tests have not been performed because the patient does not have access to them.

In multidisciplinary discussion, it is proposed surgical treatment previous alpha and beta blockage.

The presence of multiple peritoneal implants stands out from the surgical procedure, with a predominance of the visceral peritoneum, being enteric and mesial juxta in greater numbers (Figs. 1 and 2). It was performed a complete resection without macroscopic remnants (Fig. 3) with a favorable postoperative evolution.

In quarterly control, slight rise of metanephrines without accompanying symptoms.

Assessment was completed with PET-CT that evidenced persistence of peritoneal implant with expression of somatostatin receptors, in close relationship with the hepatic segment 6 and of at least two mesenteric nodules up to 8 mm one of them hypercaptive.

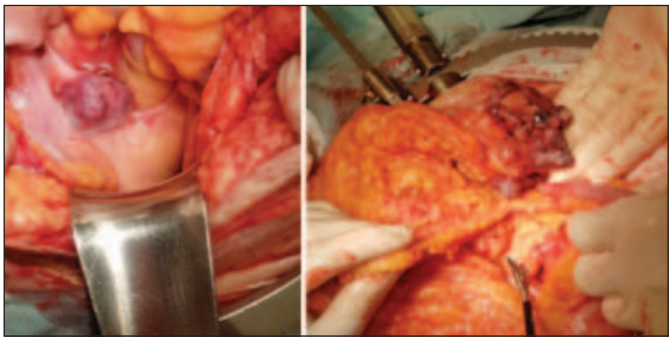

Figure 1. Multiple peritoneal implants.

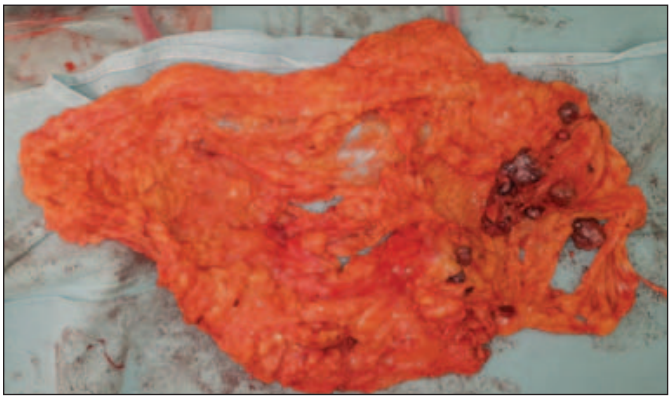

Figure 2. **Piece of resection-omentectomy**.

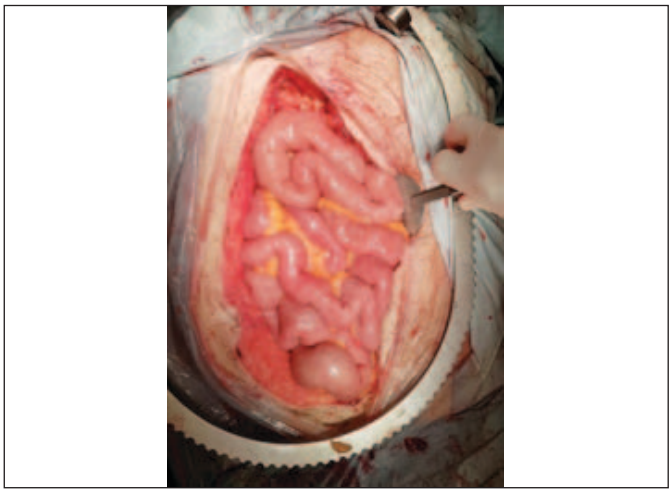

Figure 3. **Result after debulking (omentectomy and resection of all macroscopic lesion were performed).**

Consequently, he was treated with 131I-MIBG and had been monitored progress with SPECT-CT (131I MIBG) which shows a partial response to metabolic radiotherapy (Fig. 4).

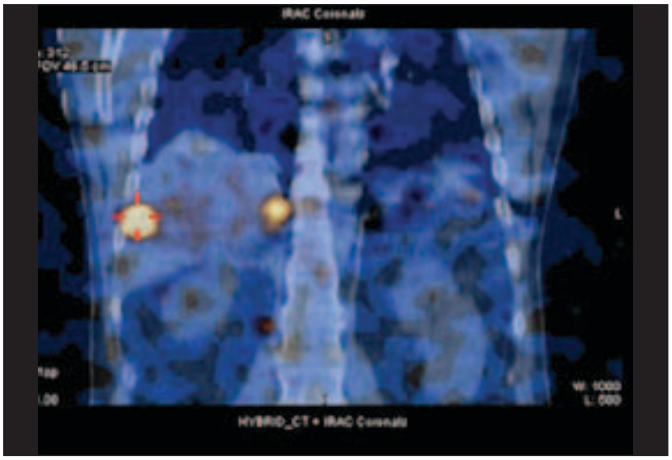

Figure 4. **MIBG con SPECT-CT (131I MIBG).**

Discussion

Approximately 10% of pheochromocytomas are malignant, with the presence of metastases at the time of diagnosis or up to 20 years later, which certifies the emergence of malignancy. The natural course of metastatic disease is very heterogeneous, with an overall survival rate at 5 years ranging between 40% and 85%, with its evolution difficult to predict.

Management of metastatic pheochromocytoma remains a challenge. So much so, that recent

Studies[8] propose that the elaboration of gene expression and methylation profiles can allow these patients to be characterized in groups with the aim of guiding therapy more effectively.

Recent work regarding the molecular characteristics of pheochromocytomas and paragangliomas reports that more than 30%-40% of them are associated with inherited genetic abnormalities involving more than 20 genes, including *SDHX*, *RET*, *VHL*, *NF1*, *TMEM127*, *MAX* and others. Such genetic alterations are primarily involved in the pathogenesis of pseudohypoxia, Wnt signaling, and kinase.[9]

Currently available therapeutic options are surgical debulking, radiopharmaceutical therapy (IMIBG, Y and Lu-DOTATATE), chemotherapy and targeted therapy. The timing at which metastatic patients benefit most from systemic therapy has not yet been established. However, at some point they will require resective surgical treatment.[10]

131IMIBG is considered today as the most effective treatment along with surgery, so that it has been recommended as a first-line treatment in patients with slow-growing metastatic lesions as well as against relapses or tumor persistence. Chemotherapy with cyclophosphamide, vincristine and dacarbazine, achieves a radiological response in half of the cases, with good hormonal response and an average survival rate of almost two years. Treatment with 177Lu-octreotide has been effective in some patients and is useful in tumors that do not capture 131I-MIBG or in combination with it as they may have a synergistic effect.

Targeted therapy with tyrosine kinase inhibitors manifests itself as a vision for the future in full development. Preliminary results from a phase II11 clinical trial with cabozantinib showed partial response/disease stabilization in 93% of the 14 patients included. Multiple early-stage clinical trials evaluate the efficacy of different therapeutic options including immunotherapy, radiopharmaceuticals and peptide receptors, seeking greater survival in this group of patients.[12]

Conclusion

Pheochromocytoma is a rare pathology, even more so its malignant presentation. It is an aggressive entity but with an acceptable survival, subject to palliative treatment with good results.

Expectant management whenever possible is a priority.

When the symptomatology is flowery and difficult to manage medically, the therapeutic range is imposed being the treatment option a combination between surgical reduction and 131I-MIBG.

Contributorship Statement / Declaração de Contribuição:

CG and UP: Conceptualization, data collection, writing original draft, and final approval.
CB: Conceptualization, methodology, supervision, review and final approval.
JB: Conceptualization, data collection, review and final approval.

Responsabilidades Éticas

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References / Referências

1. Neumann HP, Bausch B, McWhinney SR, Bender BU, Gimm O, Franke G, et al. Germ-line mutations in nonsyndromic phechromocytoma. N Engl J Med. 2002;346:1459-66. doi: 10.1056/NEJMoa020152.
2. Bravo EL, Tagle R. Pheochromocytomas: State of the art and future prospects. Endocr Rev. 2003;24:539-53. doi: 10.1210/er.2002-0013.
3. Motta-Ramirez GA, Remer EM, Herts BR Gill IS, Hamrahian AH. Comparison of CT findings in symptomatic and incidentally discovered

pheochromocytomas. AJR Am J Roentgenol. 2005;185:684-8. doi: 10.2214/ajr.185.3.01850684.

4. Dunnick NR, Korobkin M. Imaging of adrenal incidentalomas: current status. AJR Am J Roentgenol. 2002;179:559-68. doi: 10.2214/ajr.179.3.1790559.
5. Arias Martínez N, Barbado Hernández FJ, Couto Caro R, Gil Guerrero L, Coronado Poggio M, Navarro T, et al. Malignant pheochromocytoma treated with MIBG I131. An Med Intern. 2003; 8:575-8.
6. van der Harst E, de Herder WW, Bruining HA, Bonjer HJ, de Krijger RR, Lamberts SW, et al. [(123)I]metaiodobenzylguanidine and [(111)In] octreotide uptake in begnign and malignant pheochromocytomas. J Clin Endocrinol Metab. 2001;86:685-93. doi: 10.1210/jcem.86.2.7238.
7. Pacak K, Eisenhofer G, Ahlman H, Bornstein SR, GimenezRoqueplo AP, Grossman AB, et al. Pheochromocytoma: recommendations for clinical practice from the First International Symposium. Nat Clin Prac End Metab. 2007;3:92-102. doi: 10.1038/ncpendmet0396.
8. Corssmit EP, Snel M, Kapiteijn E. Malignant pheochromocytoma and paraganglioma: management options. Curr Opin Oncol. 2020;32:20-6. doi: 10.1097/CCO.0000000000000589.
9. Yamazaki Y, Gao X, Pecori A, Nakamura Y, Tezuka Y, Omata K, et al. Recent Advances in Histopathological and Molecular Diagnosis in Pheochromocytoma and Paraganglioma: Challenges for Predicting Metastasis in Individual Patients. Front Endocrinol. 2020;11:587769. doi: 10.3389/fendo.2020.587769.
10. Hescot S, Leboulleux S, Amar L, Vezzosi D, Borget I, Bournaud-Salinas C, et al. One-year progression-free survival of therapy-naive patients with malignant pheochromocytoma and paraganglioma. J Clin Endocrinol Metab. 2013;98:4006-12. doi: 10.1210/jc.2013-1907.
11. Jimenez C. A phase 2 study to evaluate the effects of cabozantinib in patients with unresectable metastatic pheo-chromocytomas and paragangliomas. Endocr Pract. 2018; 24:25.
12. Hamidi O. Metastatic pheochromocytoma and paraganglioma: recent advances in prognosis and management. Curr Opin Endocrinol Diabetes Obes. 2019;26:146-54. doi: 10.1097/MED.0000000000000476.