Clinical note

Complete hormonal and metabolic response after iodine-131 metaiodobenzylguanidine treatment in a patient diagnosed of malignant pheochromocytoma


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A B S T R A C T

Radiolabeled metaiodobenzylguanidine is an analog of norepinephrine used to localize tumors that express the neurohormone transporters, specifically those derived from the neural crest having a neuroendocrine origin. It is also used to treat non-surgical metastases derived from them. A review of the literature revealed symptomatic improvements associated to a decrease in hormone levels in a significant percentage of patients after 131I-MIBG treatment. However, complete tumor remission has been described only in very few cases and hardly ever when bone metastases exist.

We present a case of a patient diagnosed of malignant pheochromocytoma who achieved complete hormonal and metabolic response after 131I-MIBG treatment (600 mCi) in spite of the presence of bone metastases.

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R E S U M E N

La metaiodobencilguanidina radiomarcada es un análogo de la norepinefrina que se utiliza en la localización de tumores que expresan transportadores de dicha neurohormona, especialmente los derivados de la cresta neural y de origen neuroendocrino, y en el tratamiento de sus metástasis cuando estas no son quirúrgicas. En la literatura revisada se encuentran mejorías sintomáticas, asociadas a un descenso en los niveles hormonales, en un porcentaje no despreciable de casos tras el tratamiento con 131I-MIBG. Sin embargo, la remisión tumoral completa se ha descrito en muy pocas ocasiones y casi nunca en presencia de metástasis óseas.

Presentamos un caso de feocromocitoma maligno que tras el tratamiento con 131I-MIBG (600 mCi) alcanzó una respuesta hormonal y metabólica completa a pesar de la existencia de metástasis óseas.

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Introduction

Pheochromocytoma is a catecholamine producing tumor originating in the chromaffin cells of the adrenal glands. Metaiodobenzylguanidine (MIBG) is an analog of guanetidine with a structure which is very similar to that of norepinephrine in that, when labeled with radioactive isotopes, it is converted into a radiotracer allowing images of the sympathetic nervous system to be obtained, being taken up in the vesicles of adrenergic storage.

Scintigraphic studies with MIBG present a high sensitivity of greater than 90% and a specificity of close to 100% in the diagnosis of pheochromocytoma. It has been reported that only 10% of these tumors are malignant, however, 50% develop metastasis 5 years after diagnosis, thereby suggesting that the potential of malignancy of these tumors is underestimated. There are no histological or biochemical criteria to determine the malignancy of this tumor. It is only diagnosed on the demonstration of tumoral tissue in localizations in which, in normal conditions, there are no chromaffin cells, mainly in bone, the liver, lung and in the lymph nodes. The treatment of choice is surgery of both the primary tumor and the metastases and possible recurrences. When surgery is not possible, palliative treatment with radiometabolic therapy or combined chemotherapy may be used. Few cases with complete remission have been described in the literature. The patient presented herewith achieved complete biochemical and metabolic response following therapy with 131I-MIBG.

Clinical case

A 20-year-old male patient was studied for self-limiting episodes of palpitations, diaphoresis, tremor, pulsating headache, and arterial hypertension. Biochemical analysis demonstrated an
Table 1
Analytical evolution along the disease.

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<thead>
<tr>
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<tr>
<td>At D</td>
<td>475 μg/24 h</td>
<td></td>
<td>1.957 μg/24 h</td>
<td></td>
</tr>
<tr>
<td>After</td>
<td>90 μg/24 h</td>
<td></td>
<td>424 μg/24 h</td>
<td></td>
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<tr>
<td>2 years after S</td>
<td>895 μg/24 h</td>
<td>506 μg/g</td>
<td>1.878 μg/24 h</td>
<td>1.061 μg/g</td>
</tr>
<tr>
<td>3 m after 131I-MIBG ttm</td>
<td>670 μg/24 h</td>
<td>311 μg/g</td>
<td>1.821 μg/24 h</td>
<td>845 μg/g</td>
</tr>
<tr>
<td>6 months after 131I-MIBG ttm</td>
<td>506 μg/24 h</td>
<td>233 μg/g</td>
<td>1.048 μg/24 h</td>
<td>484 μg/g</td>
</tr>
<tr>
<td>9 months after 131I-MIBG ttm</td>
<td>431 μg/24 h</td>
<td>206 μg/g</td>
<td>873 μg/24 h</td>
<td>417 μg/g</td>
</tr>
<tr>
<td>12 months after 131I-MIBG ttm</td>
<td>185 μg/24 h</td>
<td>106 μg/g</td>
<td>342 μg/24 h</td>
<td>196 μg/g</td>
</tr>
<tr>
<td>2 years after 131I-MIBG ttm</td>
<td>335 μg/24 h</td>
<td>131 μg/g</td>
<td>591 μg/24 h</td>
<td>230 μg/g</td>
</tr>
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Elevation in the metanephrines in urine (Table 1). Magnetic resonance (MR) imaging showed a 4 cm right adrenal mass and scintigraphy with 123I-MIBG showed pathological uptake of the radiotracer in this adrenal mass, achieving a diagnosis of pheochromocytoma (Fig. 1). In view of these findings the patient underwent surgery with histological confirmation of the suspected diagnosis.

Following 2 asymptomatic years, the urinary metanephrines again rose (Table 1) and another scintigraphy with 123I-MIBG - MIBG was performed showing multiple pathological deposits of the radiotracer, indicating pathologic chromaffin-dependent tissue in the right frontal region, in the mid anterior and posterior line of the thorax, in the right hemithorax, in the proximal and posterior third of the abdomen and multiple deposits in both hemipelvis and in the theoretical area of the right femur compatible with metastasis of pheochromocytoma (the precise sites could not be specified for lack of a SPECT/CT) (Fig. 2). The CT carried out to complete the study showed lithic lesions in different bone structures. A scan with 111In-octreotide was also undertaken but did not show any significant alterations.

In the presence of metastases taking up 123I-MIBG, radiometabolic therapy with 200 mCi de 131I-MIBG was performed. The post-dose scan visualized more lesions than in the diagnostic image with 123I-MIBG (Fig. 3).

One and 4 months after the first therapeutic dose, another 2 treatments with 131I-MIBG were administered following the same protocol and previous analyses to discard hematologic alterations contraindicating the administration of these treatments.

Twelve months after the radiometabolic therapy chromatogranine A, metanephrines in urine (Table 1) and the scan with 123I-MIBG normalized and the CT only visualized “minimum sclerosis in the areas in which the previous images were compatible with metastasis” (Fig. 4), achieving complete biochemical and metabolic response. Two years after the completion of the treatment with 131I-MIBG the patient continues asymptomatic, the chromatogranine A and the metanephrines in urine are normal and the scan with 123I-MIBG is negative.

Discussion

Extensive experience has been reported on the ability of 123I-MIBG to localize tumors derived from the neural crest. Most work groups coincide in that scintigraphy with 123I-MIBG is not a screening method for the diagnosis of tumors derived from chromaffin tissue; in the presence of clinical and biochemical suspicion they are usually diagnosed by CT or MR. 123I Scintigraphy with 123I-MIBG is useful particularly when the morphologic techniques are indeterminate (providing functional information of the lesion), for the diagnosis of unsuspected metastasis, the diagnosis of paragangliomas, in the study of familial syndromes, on suspicion of partial surgical resection or tumor recurrence, and in the annual follow up of these patients.

Precise localization of the lesions by metabolic imaging is difficult, at times being essential in view of therapy. The introduction of hybrid SPECT/CT equipment has solved this problem since it provides better anatomical localization than SPECT and detects unknown lesions by planar imaging with 123I-MIBG.5

The use of MIBG labeled with 131Iodine (beta and gamma emitters) for the treatment of malignant pheochromocytomas began in 1983 when Sisson et al. described their initial experience.2 The objective of treatment is palliative with the intention of relieving...
the symptoms, reduce the secretion of catecholamines, reduce blood pressure and detain, and even reverse, tumor progression, all with scarce secondary effects, particularly with respect to bone marrow toxicity. There are no uniform criteria with regard to the selection of patients with unresectable pheochromocytoma for radiometabolic therapy with $^{131}$I-MIBG, although it is clear that the presence of sufficient uptake of MIBG with diagnostic doses and ruling out the presence of uptake in the lesions of high risk such as those causing spinal cord compression are essential requirements. On the other hand, post-dose therapeutic scintigraphy has shown to be superior to diagnostic scintigraphy with $^{123}$I-MIBG with regard to the ability to detect lesions, even with SPECT/CT: thus the post-dose images are considered essential for the management of these patients.

Taking into account the neuroectodermic origin of these tumors it has been reported that up to 73% of the pheochromocytoma cells express somatostatin receptors, allowing the use of radiolabeled analogs for both diagnostic purposes ($^{111}$In-octreotide is most commonly used) and together with beta-emitting radioisotopes for radiometabolic therapy (those most used are radiolabeled with $^{90}$Y or with $^{177}$Lu). In our case, uptake in the metastatic lesions was not demonstrated on the scintigraphy with $^{111}$In-octreotide, thereby contraindicating radiometabolic therapy with somatostatin analogs.

The results obtained with combined chemotherapy (cyclophosphamide, vincristine and dacarbacin) are similar to those obtained with $^{131}$I-MIBG. However, it lacks tumor specificity and the toxicity is significantly greater and thus, treatment with $^{131}$I-MIBG is first indicated, reserving chemotherapy for patients with a negative MIBG diagnosis or with no response to treatment with $^{131}$I-MIBG.

In the literature reviewed a greater response was observed with treatment with $^{131}$I-MIBG in patients with soft-tissue metastasis, being lesser in those presenting bone involvement. However, a reduction in tumor size has been described in a few cases, and almost never in the presence of bone metastasis. In our case, complete biochemical and metabolic response was obtained after 3 doses of $^{131}$I-MIBG, despite the presence of bone metastasis. The clinical improvement was associated with hormone response which occurs in approximately 79% of the cases, and is usually not found prior to the administration of the third dose of $^{131}$I-MIBG.

According to the literature survival ranges from 9 months, in non-responders patients to treatment, to 46 months, in responders, thereby demonstrating that treatment with $^{131}$I-MIBG improves survival. In general, the 5-year survival is of 40%.
although isolated cases have survived up to even 26 years after treatment.²

It can be concluded that treatment with ¹³¹I-MIBG is, undoubtedly, an effective palliative treatment, associated with clinical improvement in a notable percentage of cases and with less toxicity than chemotherapy, achieving, in some circumstances, complete biochemical and tumor response and/or long patient survival.

References