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Multiple Endocrine Neoplasia 2A and ^{123}I-Metaiodobenzylguanidine Scintigraphy: Theranostics Based Treatment

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Abstract: *MEN IIa syndrome is diagnosed when pheochromocytoma, a medullary carcinoma of the thyroid, generally associated with an increase in calcitonin and parathyroid hyperplasia, or a tumor that generates hyperparathyroidism are present. Pheochromocytoma is a catecholamine-secreting neuro-ectodermal tumor that originates from chromaffin cells in the adrenal medulla or from extra-adrenal chromaffin tissues, such as ganglions and sympathetic paraganglia. The neuroendocrine system is able to incorporate amine precursors with subsequent decarboxylation, as it derives from a family of cells originating in the neural crest. ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy is a proven reliable noninvasive technique for prompt confirmation of catecholamine releasing tumors. Labelling MIBG with ^{131}Iodine, this radiopharmaceutical could be used as a radiotherapeutic metabolic agent in neuroectodermal tumors. 123I-MIBG is useful for diagnostic purpose, but not suited for therapy; using 131I, that contain β-particles with therapeutic effect, theranostics principles are respected.*

Keywords: *pheocromocytoma, medullary carcinoma, theranostics, molecular radiotherapy*

1. Introduction

Pheochromocytoma is a catecholamine-secreting neuro-ectodermal tumor that originates from chromaffin cells in the adrenal medulla or from extra-adrenal chromaffin tissues, such as ganglions and sympathetic paraganglia. The latter are normally located both along the course of the vascular bundle in the neck (parasympathetic ganglia) and along the course of the large thoracic and abdominal vessels (sympathetic ganglia) [1]. It occurs equally in both sexes and can occur at any age; 10% of pheochromocytomas appear in the pediatric age, but the maximum incidence is observed in between 30 and 50 years old patients and is present in about 0.1% of hypertensive subjects. 90% of pheochromocytomas are adrenal and in any case 90% of extra-adrenal forms are located in the abdominal area; sometimes it is bilateral (10%) and has a low frequency of malignancy [2].

The tumor may present as sporadic or as a component of genetically transmitted syndrome. MEN IIa syndrome is diagnosed when pheochromocytoma, medullary carcinoma of the thyroid, associated with an increase in calcitonin, and parathyroid hyperplasia, or a tumor that generates hyperparathyroidism, are present. While familiarity was reported up to the early 2000s in 10% of cases, more recent studies have instead shown that the onset of pheo-chromocytoma is linked to various types of germline mutations. Some examples are the von Hippel-Lindau (VHL gene), the Multiple Endocrine Neoplasia type 2 (associated with RET gene) and neurofibromatosis type 1 (linked to NF-1 gene) [3].

And again the genes encoding the B, C and D subunits of mitochondrial succinodehydrogenase (SDH) that are associated with syndromes with pheochromocytoma and/or paraganglioma, named PGL4, PGL3 and PGL1 respectively [3].

The diagnosis is performed with imaging techniques, CT, MRI, Ultrasound [4, 5].

2. Brief History of MIBG-Scintigraphy

The neuroendocrine system is able to incorporate amine precursors with subsequent decarboxylation, as it derives from a family of cells originating in the neural crest.

In a 1983 paper [6], ^{131}l-MIBG (metaiodobenzylguanidine) [7], an adrenergic tissue-localizing radiotracer, has been used for diagnosis of pheochromocytoma. The same group [8] in a 400 subject's series found sensitive to be 78.4% in primary, sporadic pheochromocytoma, 92.4% in malignant pheochromocytoma, and 94.3% in familial pheochromocytoma giving an overall sensitivity of 87.4%.

The specificity was 98.9% in primary, sporadic pheochromocytoma, 100% in malignant pheochromocytoma, and 100% in familial pheochromocytoma. The overall specificity was 98.9%.

So radio iodinated MIBG scintigraphy is the most common functional imaging technique used in the evaluation of pheochromocytoma. This molecule can be radiolabeled with ^{131}Iodine or ^{123}Iodine. The difference is that the former contains β-particles with high tissue damage and low resolution power of scintigraphic images, due to the low dose that can be administered for therapeutic purposes only. The other one can only be used for diagnostic purposes as its physical characteristics, with a rather low half-life (13.2 hours against about 8 days of ^{131}I) and for its decay energy (only γ-rays at (low) 159 keV), make it rather good from the point of view of the patient's radiation protection. For these reasons ^{123}I-metaiodobenzylguanidine (^{123}I-MIBG) scintigraphy is a proven reliable noninvasive technique for prompt confirmation of catecholamine releasing tumors [9-11].

The radiopharmaceutical is an analogue of norepinephrine and from a diagnostic point of view in literature the method has a sensitivity of 77-90% and a specificity of 95-100% [12, 13]. It is known that may be present false positives for the physiological uptake of the adrenal glands or small lesions that are not highlighted. In case of low localization of MIBG the hybrid SPECT/CT technique [14], can help to define the anatomical position of these lesions [15]. In these cases, the SPECT/CT with ^{123}I-MIBG is able to provide both anatomical and functional information with improved sensitivity and specificity (Fig1) if compared to planar or total-body technique (Fig2), allowing better definition and localization of neoplastic lesions, in order to distinguish between small tumors and physiological or pathological uptake, confirming scintigraphy with MIBG as a safe, effective and non-invasive method, with advantage of tissue specificity and ability to investigate the whole body, thus demonstrating MIBG concentrantion both in adrenal and in thyroid (Fig3), typical of MEN 2A Syndrome. Even in patients whose CT or MRI have shown the presence of an adrenal tumor, the MIBG investigation can confirm that the tumor is a pheochromocytoma or view extra adrenal or multifocal tumor or a disease secondary location [16].

3. ^{131}I-MIBG RADIOTHERAPY

As said before, labelling MIBG with ^{131}Iodine, this radiopharmaceutical, could be used as a radiotherapeutic metabolic agent in neuroectodermal tumors [17].

A precise measurement of the activity of radionuclides in the sites of interest is the basis of a correct dosimetric evaluation for the use of radiopharmaceuticals in nuclear medicine. The activity of ^{123}I-MIBG measured by two-dimensional scintigraphic images or, better, by SPECT tomography [18], is used to calculate the dose received by the affected tissues. Three-dimensional imaging is preferred when multiple layers are superimposed on the scintigraphic images [19]. In our previous paper an innovative iterative threshold method for tumor segmentation was proposed and implemented for a SPECT system [20].

The possibility of administering a radiopharmaceutical capable of concentrating in the lesion, labeled with a gamma emitter (^{123}I), isotope useful for detection with diagnostic equipment (SPECT), allows calculating the quantity of dose received. In this way it will be possible to calculate the exact dose to be administered of the same molecule, labeling it with a beta particle emitter for therapeutic purposes (^{131}I)

For what has been said before the real added value of this technique is obtained when a Medical-Nuclear treatment with 131I-MIBG has been planned. The essential requirement of this therapy is in fact the effective demonstration of intense uptake of metaiodobenzylguanidine by neoplastic lesions. Theranostic technology is thus applied [21]. Through the diagnostic investigation carried out with 123I-MIBG not only the exact diagnosis on the nature of the lesion is made, but also the intensity of uptake of the metaiodobenzylguanidine is assessed.

As it is known in molecular radiotherapy, made by radiopharmaceuticals administration, the dosimetric evaluation can take place either after treatment, to evaluate the real effectiveness of

the treatment, or before treatment, to determine the maximum tolerated activity to limit irradiation of healthy tissue. [21]. Thus, substituting 123I is useful for diagnostic purpose, but not for therapy. With 131I, that contain β-particles with therapeutic effect, theranostics principles are respected [22].

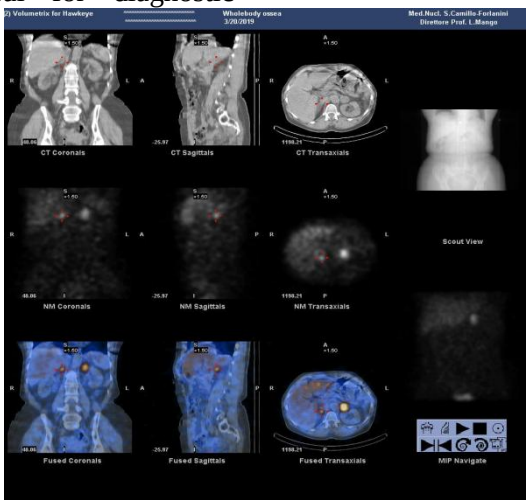

Fig1. *Abdomen SPECT/CT acquisition 24h after MIBG administration*

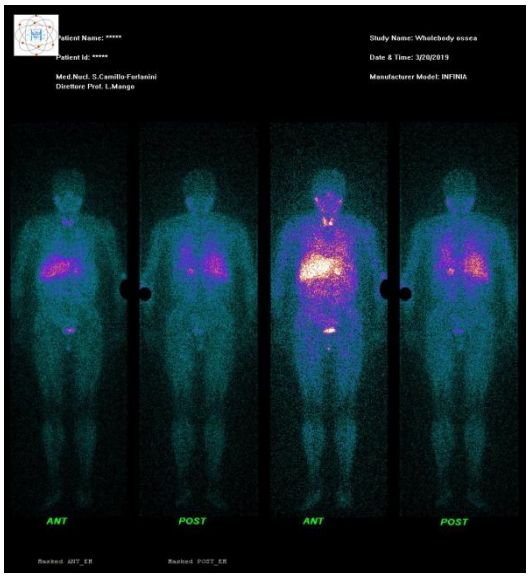

Fig2. *Whole Body acquisition 24h after MIBG administration*

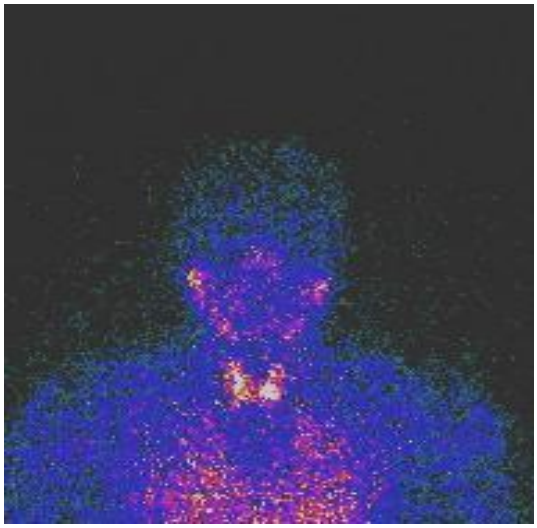

Fig3. *Thyroid scans 24h after MIBG administration (arrow indicates medullary carcinoma)*

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