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Case report

From Pulsing Headache to Pheochromocytoma: The First Application of ^{123}I-MIBG in the Scintigraphy in Croatia – A Case Report

Tatjana Bačun[1,2], Aleksandar Kibel[1,2], Ivan Mihaljević[2,3], Vlado Wagenhofer[2,3], Maja Starčević[4], Ljubica Glavaš-Obrovac[2,3]

[1]Internal Medicine Clinic, University Hospital Centre Osijek, Osijek, Croatia
[2]J. J. Strossmayer University of Osijek, School of Medicine, Osijek, Croatia
[3]Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Centre Osijek, Osijek, Croatia
[4]Technical School and Secondary Natural School Ruđer Bošković, Osijek, Croatia

ABSTRACT

This case report presents a patient with pheocromocytoma and the first use of ^{123}I-MIBG scintigraphy in the diagnostic workup of an adrenal gland tumor with elevated metanephrine and normetanephrine levels in Croatia. The patient had intensive pulsing headaches for a year. A tumour of the right suprarenal gland has been observed by ultrasound, by CT scan, and by MRI of the abdomen. A comprehensive endocrinological observation revealed significantly increased values of metanephrine, normetanephrine, epinephrine and noreinephrine. ^{123}I-MIBG scintigraphy excluded multiple tumours and metastases of malignant pheochromocytoma. After surgery, diagnosis of pheochromocytoma was proven histologically. Three weeks after surgery, the values of metanephrine and normetanephrine were within the normal range.

Keywords: *pheochromocytoma, headache, hypertension, catecholamine, scintigraphy*

Introduction

Pheochromocytoma

Pheochromocytoma is a rare neuroendocrine tumor derived from chromaffin cells of the sympathoadrenal system, with the majority arising in the adrenal medulla[1, 2]. When such tumors arise outside of the adrenal gland, they are termed extra-adrenal pheochromocytomas, or paragangliomas, and can be located in the abdomen, mediastinum, neck, pelvis, organ of Zuckerkandl, and other sites[1]. Pheochromocytomas secrete excessive amounts of catecholamines, leading to rapid rise and fall in blood pressure, headache, sweating and palpitations, but can also have very variable and atypical manifestations[3], which can cause substantial diagnostic difficulties. Because of excessive catecholamine secretion, pheochromocytomas may precipitate life-threatening hypertension or cardiac arrhythmias. These rare tumors are responsible for approximately 0.5 percent of secondary hypertension[4]. Therefore, if the diagnosis of a pheochromocytoma is overlooked, the consequences could be disastrous, even fatal[4–7]. Approximately 10 percent of pheochromocytomas and 15 to 35 percent of paragangliomas are malignant, carrying a poor prognosis[1]. Pheochromocytoma can also be associated with multiple endocrine neoplasia (MEN) syndromes, von Hippel-Lindau disease, nerofibromatosis type 1, Carney–Stratakis syndome, the recently defined paraganglioma syndomes type 1, 3 and 4 and others[8]. To tackle the task of correctly diagnosing pheochromocytoma, several laboratory tests (the most useful being plasma free metanephrine levels) and imaging techniques (computed tomography, magnetic resonance imaging etc.) are being used. But after anatomical imaging, functional imaging is increasingly being considered as an important and helpful diagnostic tool[6,9,10]. Our presented case report discusses the first experience of using ^{123}I-metaiodobenzylguanidine scintigraphy in the diagnosis of pheochromocytoma in Croatia and demonstrates the usefulness of this method in diagnostic evaluation of adrenal gland tumours.

^{123}I- MIBG scintigraphy

^{123}I-metaiodobenzylguanidine (^{123}I- MIBG) is an analog of the false neurotransmitter guanethidine and demon-

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strates high uptake both in normal sympathetically innervated tissues (such as the heart and salivary glands) and in tumors that express neurohormone transporters (neural crest and neuroendocrine tumors) [7]. It accumultes more rapidly in pheochromocytoma then in normal tissue[1]. ^{123}I-MIBG scintigraphy has a sensitivity and specificity greater then 90 percent for detection of pheochromocytoma[7] and is also very helpful in localizing extraadrenal pheochromocytomas and in following patients with malignant tumors[1]. If uptake of the radiopharmaceutical is low or absent in the case of pheocromocytoma, it is highly suggestive for malignancy, but a high accumulation on the other hand does not necessarily exclude malignancy[1]. ^{123}I-MIBG is superior in diagnostic imaging compared to ^{131}I-MIBG because of a shorter half life of ^{123}I, a lower energy of the primary imaging photon and a lack of ß-particle emission[7]. This contributes to better imaging quality and significantly lower radiation dose.

Clinical Case

The presented patient is a 34-year-old woman, who had not been severely ill before the treatment. Family medical history included the mother suffering from hypertension and the father having elevated cholesterol levels. Personal medical history revealed an appendectomy at the age of 6 years and a left vocal cord polyp surgery 2 years ago. 16 months before final diagnosis was made, the patient complained about intensive pulsing headaches followed by redness and warmth of the face which spread through the body. The measured blood pressure was 150/110 mmHg. During a period of ten months after this initial presentation, the patient had no substantial complaints and did not measure her blood pressure. However, after this period the initial symptoms returned, with palpitations, tachycardia, fine tremor of extremities and general increase in sweating. Thyroid gland workup was performed, with normal results. The patient was examined by an endocrinologist who recommended further workup, but the patient did not comply with this recommendation. She was, among others, referred also to a psychiatrist, but declined to consult him.

Three months after that the episodes became more frequent, occasionally up to 2 times /day with blood pressure levels of up to 180/110 mmHg, but more often up to 150/110 mmHg, because of which she was frequently seeking assistance at the Department of emergency medicine. Between these episodes, blood pressure levels were normal (120/80 mmHg). More than a month later, an ultrasonography of the abdomen was performed and a round expansive mass was detected in the right liver lobe with dimensions 6.5 x 5 cm, partly hyperechogenic, partly anechogenic, compressing the bile bladder. A computed tomographic scan (CT) of the abdomen showed an oval expansive, partly cystic, formation, with dimensions 6x5 cm, ranging from the 6th liver segment caudally and occupying the most part of the right suprarenal compartment (Figure 1a). The central cystic parts were septate, with the outer regions of the solid mass. After applying contrast, the outer solid parts of the mass were enhanced, whereas the inner cystic regions remained hypodense. The possibility of an echinococcal (hydatid) cyst was assumed, but excluded by magnetic resonance imaging (MRI). The MRI showed an oval, mostly hiperintensive and only marginally hypointensive zone in the suprarenal area, with irregular endoluminal growths (Figure 1b). On post-contrast images it was directly enhanced with dimensions 5.4 x 4.9 cm. Afterwards, the patient was admitted to our hospital, a tertiary centre, because of endocrinological workup.

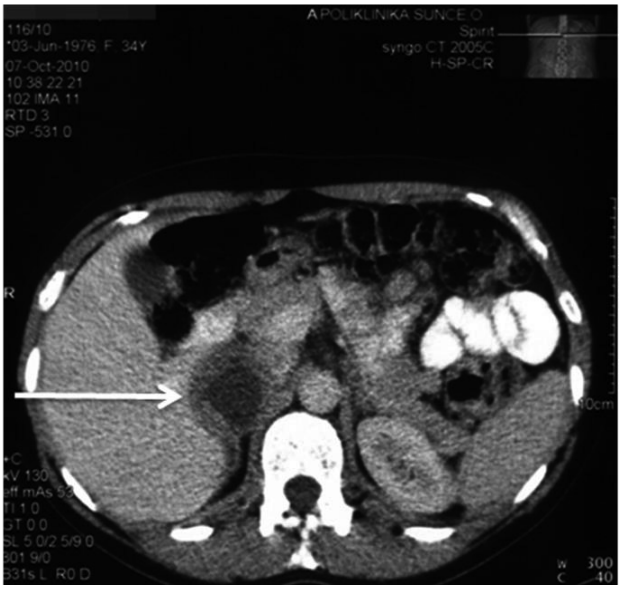

Fig. 1a. CT scan of the abdomen showing an expansive formation ranging from the 6th liver segment caudally and occupying the most part of the right suprarenal compartment.

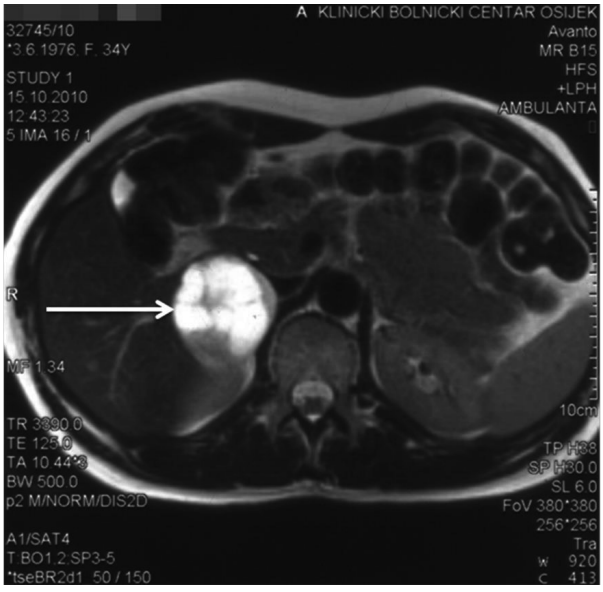

Fig. 1b. MRI of the abdomen, showing an oval, mostly hiperintensive and only marginally hypointensive zone in the suprarenal area.

After adequate preparation, the values of metanephrine, normetanephrine, epinephrine, noreinephrine and vanillylmandelic acid (VMA) were significantly elevated (with the levels of metanephrine and normetanephrine more than 12 times above normal), which suggested the diagnosis of pheochromocytoma. Other endocrinological test results were within normal ranges (including chromogranin and neuron specific enolase), the basic laboratory parameters and the chest X-ray were normal, and so was the CT scan of the chest. ^{123}I-metaiodobenzylguanidine scintigraphy (^{123}I- MIBG) was conducted, rerpresenting the first experience of scanning of a neuroendocrinological tumor with the mentioned radiopharmaceutical in Croatia and the Clinical Institute of Nuclear Medicine and Radiation Protection in University Hospital Centre Osijek. The following imaging protocol was used: 1. preparation – thyroid blockade 30 minutes before injection (preventing radioiodine uptake in the thyroid); 2. administration: slow injection (1–2 minutes) of 370 MBq (±10%) ^{123}I-MIBG; 3. imaging: acquisition at 15 min and 4 h post-injection, planar images: 128 x 128 matrix, 10 minute acquisition, SPECT images: 64 x 64 matrix, 64 frame, 30 s/slice, 159 keV photopeak (20% window), single head camera, LEHR collimator.

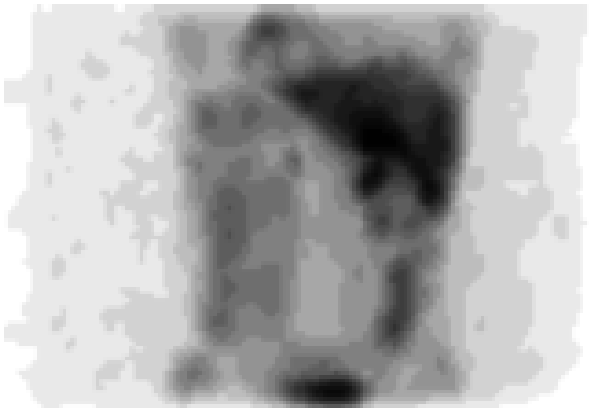

Fig. 2a. Adrenal gland scintigraphy using 123I-MIBG. Pathological accumulation of activity from the 3rd liver segment through porta hepatis to the caudal, oval shaped, not quite homogeneous aggregation, with "cold" areas - may indicate the presence of pheochromocytoma.

The ^{123}I- MIBG accumulation was detectable in the area of the right suprarenal gland, confirming the existence of pheochromocytoma. Figure 2a shows a selected image of the pathological radiopharmaceutical accumulations, and Figure 2b shows the SPECT imaging from different angles.

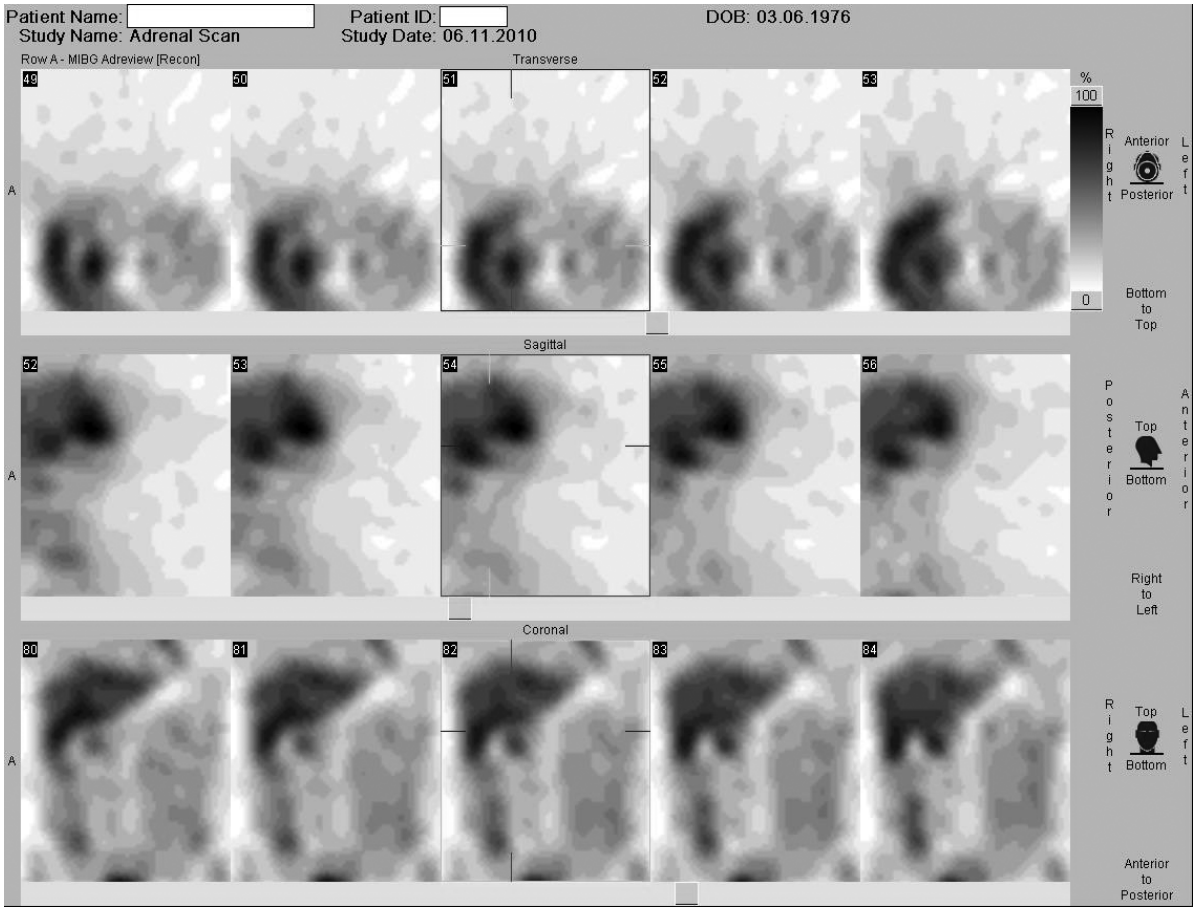

Fig. 2b. Adrenal gland scintigraphy using ^{123}I-MIBG. Sequence of SPECT images.

During preoperative treatment, α- and ß-adrenergic blockade (fenoxybenzamine and bisoprolol) was included to control blood pressure and to prevent hypertensive crises. On the second day, patient was encouraged to start a diet high in sodium content (5 g daily) to expand the contracted blood volume. During hospitalization, the patient had frequent attacks with the blood pressure up to 180/95 mmHg; after the introduction of alpha blockade, during the attacks the values did not go higher than 150/90 mmHg, while between the attacks the values were in the range 100–120/70–80 mmHg. She was surgically treated at the Urology Clinic of University Hospital Centre Zagreb. Diagnosis of pheochromocytoma was confirmed histologically, and removed lymph nodes from the abdomen were histologically normal. Three weeks after surgery, the values of metanephrine and normetanephrine were within normal limits. The patient was feeling well. She returned to work one month after the operation. It is planned to monitor the values of metanephrine and normetanephrine once a year during the next 10 years. Genetic testing for RET proto-oncogene mutations is under way.

Conclusion

^{123}I-MIBG scintigraphy proved to be a useful method in the diagnosis of pheochromocytoma in our presented case. It confirmed that the adrenal gland tumour in question accumulated the radiopharmaceutical and was indeed a pheochromocytoma, as suspected on the basis of biochemical tests and a visible suprarenal mass with a diameter of approximately 6 cm. This was at the same time the first performed ^{123}I-MIBG scintigraphy in the Clinical Institute of Nuclear Medicine and Radiation Protection, University Hospital Centre Osijek, to confirm pheochromocytoma developed in a 34-year-old woman. This method is not only relevant in confirming suspicious masses of the adrenal glands, but can also be important in localizing tumour tissue outside of the adrenal glands (paragangliomas), as well as in determining metastases of pheochromocytoma, which would confirm malignancy. In fact, it may be quite important to differentiate paraganglioma from adrenal gland pheochromocytoma (not feasible based on biochemical testing), since recent analyses suggest differences in genetic mutations, invasiveness and therapy for the two tumour variants[11].

After the proper diagnostic algorithm was implemented and the diagnosis confirmed, the patient was treated successfully, with the values of metanephrine and normetanephrine reaching the normal range three weeks after surgery. She has been monitored since for possible recurrence of the disease or for possible proto-oncogene mutations. The role of ^{123}I-MIBG scintigraphy may as well prove to be relevant for the follow-up of the patient, although the exact frequency of scans remains to be discussed.

This case report is also interesting because of the fact that the patient was having pulsing headaches with no clear cause recognized in the beginning. She had symptoms over a long period of time and was referred to various specialists and diagnostic procedures without receiving a conclusive diagnosis early in the workup process. It is an example that in cases of headaches, especially if diverse or unclear additional symptoms are associated with it, a clinician should always take a possible pheochromocytoma into consideration. The question of including metanephrine and normetanephrine tests into standard guidelines for headache diagnosis and workup should perhaps be evaluated in the future.

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T. Bačun

Dept. of Endocrinology, Internal Medicine Clinic, University Hospital Centre Osijek, J. J. Strossmayer University of Osijek, School of Medicine, J. Huttlera 4, Osijek, Croatia

e-mail: tatjana.bacun@os.t-com.hr

OD PULSIRAJUĆE GLAVOBOLJE DO FEOKROMOCITOMA: PRVA SCINTIGRAFIJA PRIMJENOM ^{123}I-MIBG U HRVATSKOJ – PRIKAZ SLUČAJA

S A Ž E T A K

Prikazana je bolesnica s feokromocitom i prva scintigrafija primjenom ^{123}I-MIBG u našoj ustanovi i u Hrvatskoj u dijagnostičkoj obradi tumora nadbubrežne žlijezde s povišenim vrijednostima metanefrina i normetanefrina. Bolesnica je godinu dana imala intenzivne pulsirajuće glavobolje. Ultrazvukom, CT-om i MR-om trbuha utvrđen je tumor desne nadbubrežne žlijezde. Opsežnom endokrinološkom obradom utvrđene su povišene vrijednosti metanefrina, normetanefrina, adrenalina i noradrenalina. Scintigrafijom ^{123}I-MIBG isključeni su multipli tumori i metastaze malignog feokromocitoma. Nakon operacije, dijagnoza feokromocitoma potvrđena je histološki. Tri tjedna nakon operativnog zahvata, vrijednosti metanefrina i normetanefrina bile su uredne.