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PICTORIAL ESSAY

False iodine-131 MIBG scintigraphy findings in adrenal tumors: correlation with MR imaging

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Abstract
In this study, we report our experience regarding the occurrence of false radionuclide findings in adrenal iodine-131 MIBG scintigraphy. We present a total of five patients in which nuclear images were false negative or positive in three and two cases, respectively, according to the standard radionuclide established criteria. In particular, the three cases of false-negative MIBG images consisted of two patients with necrotic or cystic pheochromocytomas (Cases 1 and 3) and a patient with a small pheochromocytoma (Case 2); the two cases of false-positive MIBG imaging consisted of a patient with an adenoma showing intense tracer uptake and of a large primary necrotic carcinoma with heterogeneous tracer concentration.

Keywords Iodine-131 · MIBG · False-negative images · False-positive images · Adrenal tumors · Pheochromocytoma

Introduction

The imaging evaluation of tumors in adrenals is one of the main clinical topic using diagnostic techniques, particularly for the increased detection of adrenal lesions using tomographic modalities as ultrasound, computed tomography (CT) and magnetic resonance (MR); in particular, these tomographic scans offer anatomic assessment of adrenal masses as well as its characterization [1]. On the other hand, nuclear medicine adrenal procedures with radiopharmaceuticals are able to provide functional evaluation of such tumors [2]. For this purpose, several radiopharmaceuticals have been proposed to characterize adrenal lesions such as norcholesterol and metaiodobenzylguanidine (MIBG), which represent the most common radioagents used in clinical practice to, respectively, identify adenoma and pheochromocytoma [2], as well as fluoro-deoxy-glucose (FDG) to detect malignant, primary and/or metastatic, adrenal masses [2]; however, false radionuclide imaging findings may occur, being misleading for tumor diagnosis [3].

The aim of the present study was to describe our experience regarding the occurrence of false scintigraphic results in adrenal iodine-131 MIBG imaging; in particular, we present a total of five patients in which radionuclide images were false negative or positive in three and two cases, respectively, according to the standard radionuclide established criteria.

Iodine-131 MIBG scintigraphy protocol

Before iodine-131 MIBG injection, thyroid iodine uptake was blocked with a saturated solution of potassium iodide (200 mg/day orally, starting 1 day before tracer administration and continuing for at least 5 days). Medical treatment with drugs potentially interfering with MIBG uptake such as opioids, tricyclic or other anti-depressants, sympathomimetics, and anti-hypertensive agents, particularly combined alpha and beta adrenoreceptor antagonists and calcium antagonists was suspended 1–3 days before tracer administration, as recommended; in case of labetalol, the drug withdrawal was performed 10 days before the procedure [3]. Iodine-131 MIBG (37 MBq; GE Healthcare) was intravenously administered. Anterior and posterior whole-body (WB) as well as anterior and posterior abdominal spot views were obtained 24, 48 and 72 h after tracer injection using a large-field-of-view gamma camera (Skylight; Philips Healthcare, Best, The Netherlands) with a high-energy collimator and a 20% window centered at 364 keV. In particular, anterior and posterior WB images were acquired with a table advancement speed of 4 cm/min, while anterior and

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posterior abdominal spot views were acquired in pre-set count modality for at least 150,000 counts for each view. For radionuclide imaging analysis, the presence of abnormally increased MIBG uptake was qualitatively evaluated in adrenal regions where tumor lesions were detected by MR according to the standard radionuclide established criteria [3]; in particular, the intensity of adrenal tumor tracer uptake was visually evaluated on high-resolution display and adrenal activity was considered abnormal when lesion tracer uptake was greater than blood pool and/or surrounding background activity as well as when no similar uptake was observed on the contralateral adrenal region.

Results

False-negative MIBG cases

Case 1. A male, 45 years old, was evaluated for arterial hypertension not pharmacologically controlled. The patient underwent abdominal Color-doppler ultrasound; no significant renal arteries blood flow abnormalities were detected; however, a round right adrenal mass, measuring 32 × 26 mm, was identified. To better characterize the adrenal lesion MR imaging was performed confirming the detection of the right adrenal tumor with inhomogeneous high signal intensity on T2 and T1 post-contrast sequences for the presence of central necrosis (Fig. 1a, b); slight drop-off signal intensity was observed on T1-weighted chemical-shift sequence. Laboratory evaluation of adrenal function showed an increased level of urinary catecholamines (448 mcg/24 h; n.v. 10–100 mcg/24 h). On the basis of abnormal catecholamines values, iodine-131 MIBG scintigraphy was performed, but no abnormal uptake was detected in the right adrenal mass (Fig. 1c). The patient had surgical resection of the lesion; histology demonstrated the presence of a cystic pheochromocytoma; hence, the result of MIBG adrenal scintigraphy was considered false negative.

Case 2. A female, 72 years old, was evaluated during the follow-up after right adrenalectomy for pheochromocytoma. Laboratory evaluation of adrenal function showed mild increase of urinary cathecholamine levels (136 mcg/24 h; n.v.10–100 mcg/24 h); thus, MR imaging was performed to evaluate the left adrenal gland and it showed the presence of a left adrenal nodule measuring 16 mm with mild hyperintensity on T2-weighted sequence, without drop-off signal intensity on T1-weighted chemical-shift sequence and with progressive contrast enhancement (Fig. 2a, b). For lesion characterization, medullary adrenal iodine-131 MIBG scintigraphy was performed, but no significant uptake was detected in the left adrenal bed (Fig. 2c). The patient had surgical resection of the left adrenal nodule; histology demonstrated the presence of pheochromocytoma; hence, the result of adrenal scintigraphy was considered as false-negative finding.

Case 3. A 29-year-old man was evaluated for clinical suspicion of multiple sclerosis; the patient had recurrent headache, decreased vision, night sweats and weight loss; arterial blood pressure was slightly increased and urinary vanillylmandelic acid (12 mg/24 h, n.v. 1.8–6.7) as well as catecholamine levels (250 pg/mL, n.v. 0–180 pg/mL) were also abnormal. The patient had a total body CT scan which showed as incidental finding a large (7 cm) left inhomogeneous bi-lobated adrenal mass characterized by a fluid anterior portion and a solid posterior region. To further characterize the adrenal mass, MRI was performed using a dedicated protocol for adrenals; an inhomogeneous, hyperintese on T2 images, large adrenal tumor was detected confirming the mixed structure of CT scan with inhomogeneous contrast enhancement on T1 scan (Fig. 3a, b). Therefore, for the suspicion of a cystic pheochromocytoma medullary adrenal scintigraphy with iodine-131 MIBG was performed, but no tracer uptake by the left adrenal mass was observed (Fig. 3c). The patient had surgical resection of the left adrenal mass; histology demonstrated a pheochromocytoma; hence, the result of MIBG scintigraphy was considered false negative.

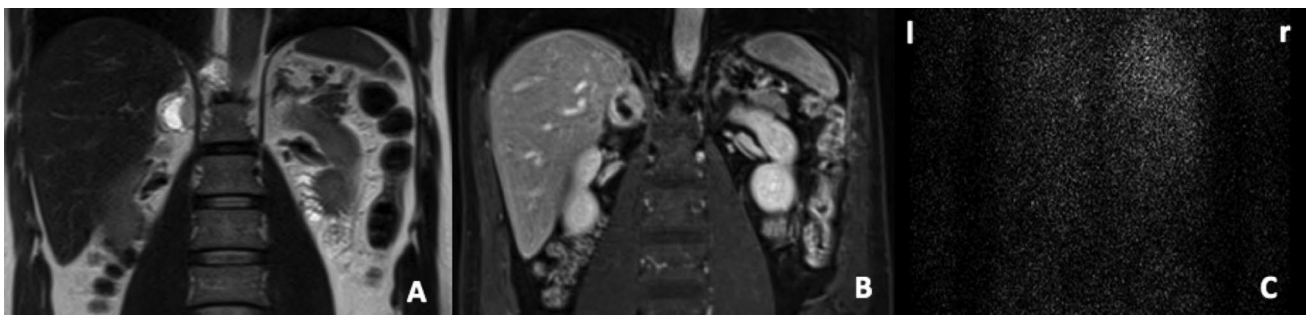

Fig. 1 Right necrotic adrenal pheochromocytoma. MR coronal scans, T2 with fat suppression (FS) and T1-enhanced FS, showed an inhomogeneous right adrenal mass with central cystic component (**a** and **b**). Planar adrenal scintigraphy with I^{131} MIBG in posterior view at 48 h after tracer injection shows no abnormal tracer uptake in the right adrenal bed (**c**)

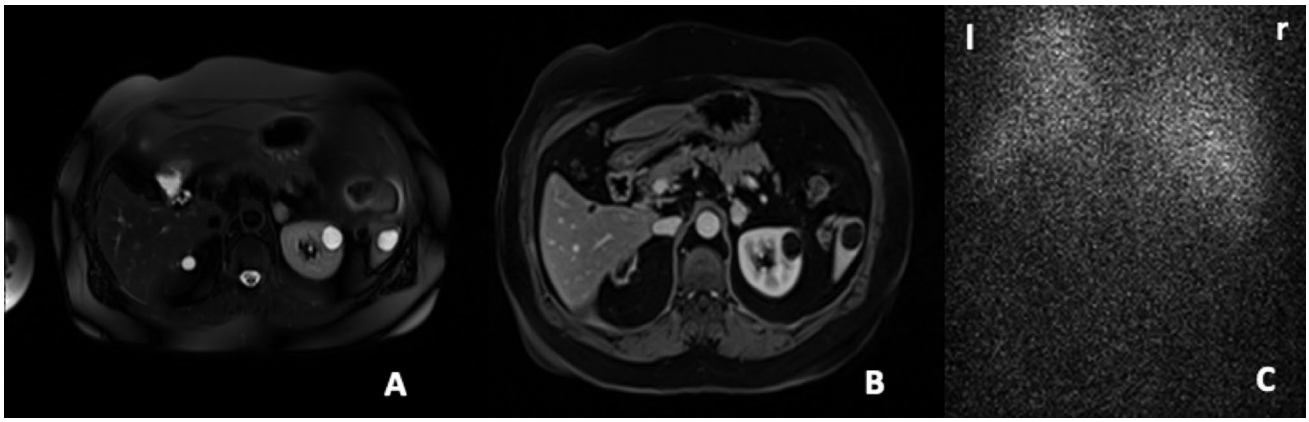

Fig. 2 Left adrenal pheochromocytoma. MR axial scans, T2 FS and T1-enhanced FS, showed a homogeneous small left adrenal nodule (**a** and **b**). Planar adrenal scintigraphy with I^{131} MIBG in posterior view at 48 h after tracer injection shows no abnormal tracer uptake in the left adrenal nodule (**c**)

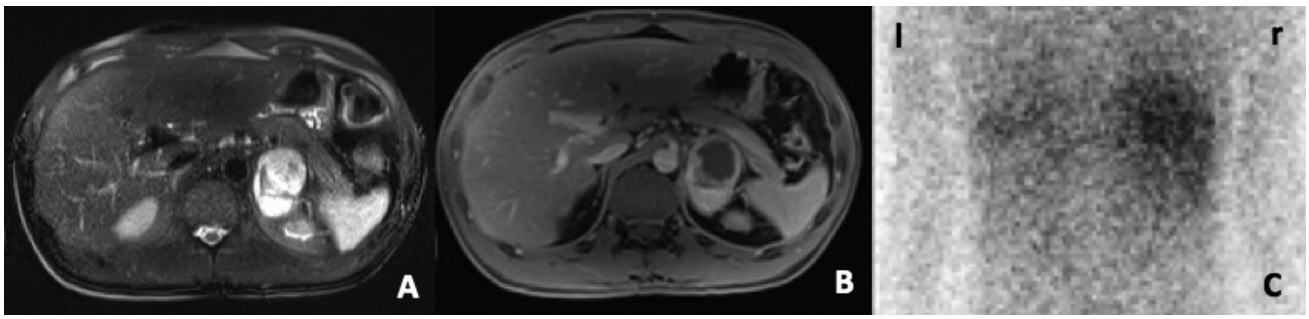

Fig. 3 Left adrenal cystic pheochromocytoma. MR axial scans, T2 FS and T1-enhanced FS, showed an inhomogeneous large left adrenal mass with bi-lobated morphology such as cystic anterior component and solid posterior tissue (**a** and **b**). Planar adrenal scintigraphy with I^{131} MIBG in posterior view at 48 h after tracer injection shows no abnormal tracer uptake in the left adrenal bed (**c**)

False-positive MIBG cases

Case 4. A 52-year-old-man with arterial hypertension was evaluated with CT to evaluate the morphology of renal arteries; however, these were normal but a solid hypodense nodule (18 mm) was detected in the left adrenal gland; the lesion was hypervascular with no significant wash-out; to characterize the lesion, MR was performed suggesting a non-adenoma, solid, T2 hyperintense as well as hyperintense tumor on T1-weighted sequence (Fig. 4a, b). Laboratory evaluation of cortical and medullary adrenal function showed only increased levels of urinary normetanephrines (675mcg/24 h; n.v. 162–527 mcg/24 h). Thus, a pheochromocytoma was suspected and medullary adrenal scintigraphy with iodine-131 MIBG was performed; increased focal tracer uptake in the left adrenal nodule was found (Fig. 4c). Therefore, on the basis of laboratory and MIBG results, a pheochromocytoma was diagnosed. Left adrenalectomy was performed, but pathology showed an adenoma; thus, MIBG finding was false positive.

Case 5. A female, 51-year-old, was evaluated to characterize a huge (12 cm) right adrenal tumor depicted by ultrasound and MR scans. The patient had clinically significant abdominal pain and increasing of arterial blood pressure (220/100 mmHg). Laboratory analysis of adrenal function was regular, but the value of urinary vanillylmandelic acid (VMA) was observed as borderline: 11.6 mg/24 h (n.v. 0–10). The tumor was situated in the right upper abdomen, probably in the retroperitoneum originating from the homolateral adrenal; in particular, the mass was inhomogeneous with a large central portion of necrosis and dislocating downward the kidney (Fig. 5a). The arterial hypertension, the large adrenal tumor and the borderline level of urinary VMA were suggestive for pheochromocytoma. For this clinical suspicion, iodine-131 MIBG scintigraphy was performed showing a large area of inhomogeneous diffuse increased activity in the right abdomen where MR located the tumor lesion (Fig. 5b). Hence, the result of MIBG scintigraphy was indicative of pheochromocytoma. The patient had surgical treatment removing a huge ($18 \times 16 \times 11$ cm),

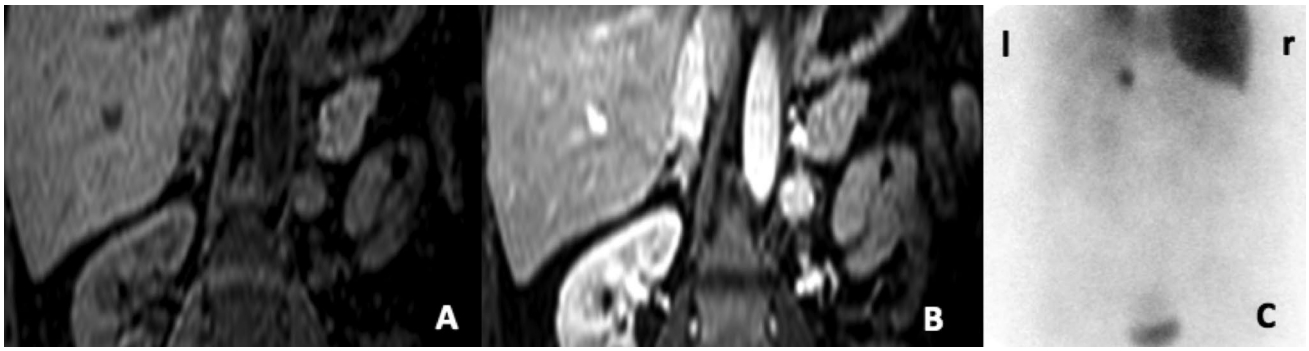

Fig. 4 Left adrenal adenoma. T1-weighted FS MR coronal scans pre- (**a**) and post- (**b**) contrast administration showed a solid homogeneous small left adrenal nodule with blurred margins located anteriorly to the upper pole of the kidney. Planar adrenal scintigraphy with I^{131} MIBG in posterior view at 48 h after tracer injection shows a focal intense tracer uptake in the left adrenal bed corresponding to the nodule detected on MR images (**c**)

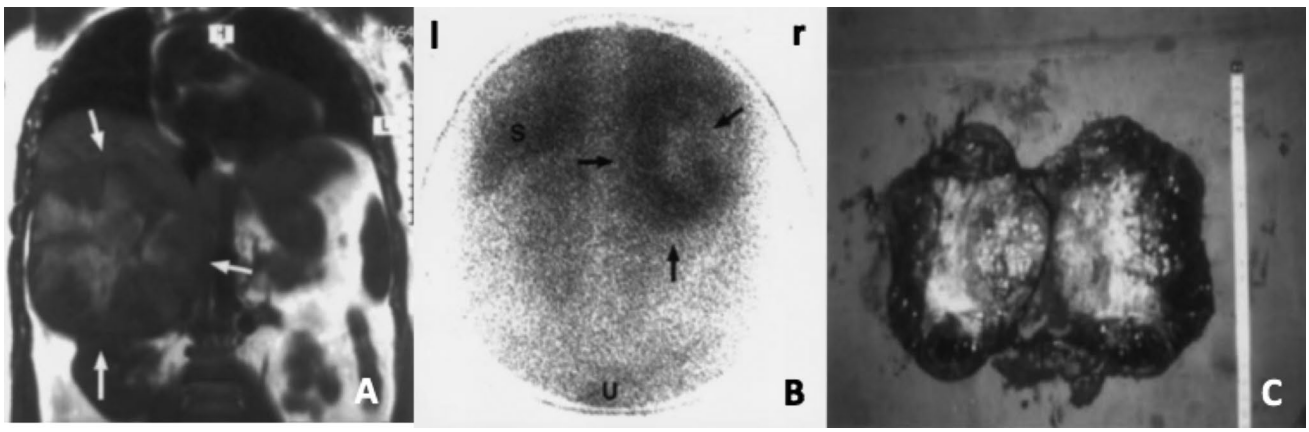

Fig. 5 Right large adrenal carcinoma. Coronal MR scan showed an inhomogeneous large right adrenal tumor (white arrows) with irregular margins and wide central intra-lesion necrosis on T1 sequence (**a**). Planar adrenal scintigraphy with I^{131} MIBG in posterior view at 48 h after tracer injection shows heterogeneous diffuse tracer uptake in the right adrenal bed (black arrows) corresponding to the large mass detected on MR image, mainly in the periphery (**b**); *S* spleen and *U* urinary bladder. Post-surgical specimen confirmed a large carcinoma with wide central intra-lesion necrosis and solid periphery (**c**); (with permission by Wolters Kluwer Health, Inc. and Copyright Clearance Center)

but well-capsulated, adrenal tumor with wide central necrosis associated with hemorrhagic degeneration. Histology proved a cortical adrenal carcinoma. The result of MIBG scintigraphy was considered false positive.

Discussion

The imaging characterization of adrenal tumors is clinically relevant in the diagnostic evaluation of patients with adrenal masses [1, 2]. Appropriate characterization of adrenal lesions is requested for correct patient care; in this setting, although the majority of incidental adrenal masses consist of benign adenomas, it is fundamental the lesion characterization for ruling out potential malignancy to ensure appropriate patient management. The diagnostic capability of CT to identify adrenal adenomas has shown usefulness because of its ability to measure attenuation, either on unenhanced or delayed enhanced images measuring contrast lesion wash-out. MRI is often used to evaluate indeterminate adrenal lesions not completely characterized by CT using chemical-shift sequence. Radionuclide adrenal imaging with specific radiotracers such as labeled nor-cholesterol, metaiodobenzylguanidine (MIBG) and fluoro-deoxyglucose (FDG) may offer significant functional information for tumor characterization enabling to, respectively, identify adrenal adenomas, pheochromocytomas and malignant adrenal tumors, both primary and metastatic [4, 5]. Positron emission tomography (PET) combined with CT has been shown to be helpful to characterize incidentally discovered

adrenal masses [6]. Although MIBG scintigraphy has been reported to be useful to characterize pheochromocytoma, the diagnostic accuracy of this radionuclide technique suffers for the occurrence of false imaging results [3].

In this study, we report our experience regarding five patients in whom the results of MIBG scan were false negative ($n=3$) or positive ($n=2$) according to the standard radionuclide established criteria [3]. The three cases of false-negative MIBG images consisted of two patients with necrotic or cystic pheochromocytomas (Cases 1 and 3) and a patient with a small pheochromocytoma (Case 2). These lesion features could explain the lack of MIBG uptake in these cases. In this regard, small tumor size, cystic lesion degeneration or necrosis and hemorrhage as well as some poorly differentiated pheochromocytomas have been reported as potential reasons of false-negative MIBG findings [3, 7]; of note, these tumor characteristics earn the epithet of "an imaging chameleon" for this lesion [8]. In details, tumor cystic degeneration may be so marked that only few identifiable cells or residual nodules may reflect the true nature of the neoplasm; moreover, wide hemorrhage followed by necrosis with cyst formation and subsequent resorption of the blood may be the likely explanation for these cystic changes [8]. In this scenario, the imaging differentiation between a simple adrenal cyst and a cystic adrenal pheochromocytoma is fundamental for correct patient management since biopsy should be avoided and surgeons should be alerted to perform adrenalectomy; for this purpose, hybrid FDG PET combined with CT or MRI might be useful for lesion characterization [9]. The small tumor size of Case 2 could justify the absence of MIBG uptake in such patient. Therefore, in false-negative MIBG cases, laboratory abnormalities and MRI features should be considered of main clinical importance for tumor diagnosis.

To date, false-negative MIBG results may also be a consequence of interfering drugs that are often necessary to control hypertension and tachyarrhythmia in patients with pheochromocytomas [10, 11]; in particular, labetalol has been reported to cause false-negative results and it should be discontinued more than 10 days before MIBG administration for study acquisition, if the patient's clinical condition allows [12]. In addition, it is needed to underline that iodine-131 is not ideal as radiolabel for MIBG scintigraphy for its unfavorable physical features such as long time of decay and high emission energy; for these reasons, its conventional radioactive dose is restrained as well as it is not preferred for tomography (SPECT) acquisition. Since iodine-131 MIBG scintigraphy has been shown to have a false-negative rate of 13% for lesion detection in pheochromocytomas, iodine-123 has been proposed as an alternative radioactive label for MIBG to improve image quality and reduce the false-negative rate [13]; in this comparative study, iodine-123 MIBG scan showed a significantly better diagnostic accuracy for pheochromocytoma lesion detection compared with iodine-131 MIBG. Thus, physical disadvantages of iodine-131 compared to the technical advantages of iodine-123, such as superior dosimetry for the shorter half-life, better detection efficacy for freedom from beta-emission, but increased gamma-emission as well as SPECT acquisition might also explain the occurrence of false-negative results of iodine-131 MIBG scintigraphy. In our experience, we selected iodine-131 MIBG as radiotracer for adrenal nuclear scanning since this radiocompound is less expensive and easily available for delivery, while iodine-123 is more expensive and produced by cyclotron [13]. SPECT acquisition may be integrated with CT using iodine-123 for an optimized scintigraphic strategy to better localized tracer uptake in adrenal regions [3], but we did not use this technical protocol because we do not have available in our department a SPECT/CT scanner. SPECT/CT with iodine-123 MIBG could be comparable to MR scanning in terms of tomographic anatomic imaging, but the functional diagnostic information of MIBG in hybrid SPECT/CT is peculiar for pheochromocytoma; conversely, although MR imaging uses multiple sequences to characterize such adrenal lesion its diagnostic performance is more limited for this purpose [14–16].

In the present experience, the two cases of false-positive MIBG imaging consisted of a patient with an adenoma showing intense tracer uptake and of a large primary carcinoma with heterogeneous tracer concentration. The possible occurrence of false-positive MIBG findings was originally described by Shapiro et al. [17] and defined as the presence of abnormal tracer uptake into tumor lesions of adrenals other than pheochromocytoma; of note, in this previous study, a case of adrenal metastasis of choriocarcinoma was reported. Successively, many cases of false-positive findings of MIBG scan have been reported in the literature [18–28]; other cases of adrenal adenomas with MIBG accumulation have been previously described by others and also by our group [18–22]; in these cases, different explanations have been provided to justify MIBG uptake by the lesions such as the coexistence within the tumor of medullary hyperplasia or the presence of dense medullary granules as well as the occurrence of collision tumors [29]. In our first false-positive MIBG Case with histologically proven adrenal adenoma, the presence within the nodule of medullary hyperplasia associated with dense medullary granules could justify the occurrence of tracer uptake. The second false-positive MIBG Case consisted of a huge adrenal carcinoma with necrotic degeneration reflected by diffuse heterogeneous tracer uptake; in this regard, similar MIBG findings are reported in the literature in several malignant adrenal lesions such as a huge carcinoma, an oncocytic carcinoma, an undifferentiated malignant tumor with rhabdoid features and a diffuse large B-cell-type lymphoma [23–26]. In these

lesions, why MIBG uptake occurred is unclear. Of note, high tumor-dependent blood flow as well as non-specific diffusional tracer uptake has been thought to be involved and these physiopathological mechanisms might justify MIBG concentration in our large tumor lesion. The potential neuroendocrine origin of specific type of adrenal carcinomas might determinate MIBG accumulation in these tumors. In detail, Miettinen et al. reported neuroendocrine differentiation, as reflected by the positivity of immunoreactivity for neurofilament proteins, S-100 protein as well as neuron-specific enolase, in adrenal carcinomas [30], even though these features were not observed in our patient. To date, MIBG uptake has been observed as false-positive results also in other benign adrenal lesions such as angiomyolipoma probably for the rich abnormal vascularization [27] as well as in a mast cell-infiltrated infantile hemangioma, in which tracer uptake was believed to be caused by increased expression of vesicular monoamine transporters by mast cells [28].

In conclusion, different tumors may occur in the adrenal glands; the knowledge of imaging features of such lesions on radiologic and radionuclide imaging will enhance the ability to make tumor characterization. In this scenario, although iodine-131 MIBG scintigraphy has been shown to be useful to characterize pheochromocytoma, the diagnostic accuracy of this nuclear technique suffers for the occurrence of false imaging results as reported in the literature and confirmed by our present experience. Future investigations might be valuable to collect potential similar radionuclide findings. Thus, MIBG scintigraphy pitfalls may occur, so that careful imaging evaluation is required for correct scan interpretation.

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Data availability Data are transparency.

Code availability Not applicable.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. This research study was conducted retrospectively from data obtained for clinical purposes. We consulted extensively with the IRB of University of Naples "Federico II" who determined that our study did not need ethical approval.

Consent to participate Informed consent was obtained from all individual participants included in the study.

Consent to publish The participant has consented to the submission of the case report to the journal.

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