Usefulness and reliability of ^{131}I-6-β-iodomethyl- nor cholesterol (NP-59), adrenal cortex scintigraphy in discrimination between adenoma and hyperplasia in case of a patient with primary hyperaldosteronism (PH) without discontinuation of antihypertension therapy

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Abstract
Clear iodine-131 (^{131}I)-6-β-iodomethyl- norcholesterol aldosterinoma finding, proven on biopsy, without prior discontinuation of spironolactone (due to high blood pressure) reveals no changes on scintigraphic sensitivity

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Case Report

An abdominal computed tomography (CT) performed on a 72 years old woman with a long history of stable hypertension (over 22 years), revealed incidentally 3 adrenal masses characterized as benign adenomas. (Two on the left adrenal gland of 2.2cm and 18cm in diameter and 1 on the right of 18cm, respectively) (Figure 1).

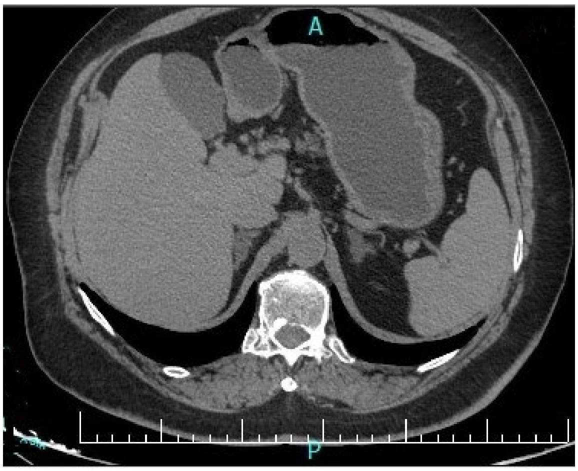

Figure 1. Abdominal CT findings: benign adenomas on both adrenal glands.

Despite multiple antihypertensive regimens, blood pressure (measuring at physician's office and at home) was consistently high and above target (<140/90mm Hg). Treatment with perindopril (10mg), amlodipine (2.5mg), indapamide (5mg), monoxidine (0.6mg/day), nebivolol 5mg/day and spironolactone (25mg) was followed. On physical examination, body weight was measured at 97kg, height at 170cm, (Body mass index: 33.6kg/m^2), blood pressure at 180/102mmHg and heart rate at 83bpm (supine position). Systemic findings were normal. Serum electrolytes showed severe hypokalemia (K^+: 2.3mEq/L). Twenty four-hour urinary potassium values were elevated (K^+: 36.40mEq/24h, Na^+: 83.2 mEq/24h). Due to persistent hypokalemia, intravenously and orally K^+ was added and spironolactone dose was increased. Complete blood count, liver and renal function tests and basal adrenocorticotropic hormone (ACTH) and cortisol levels were normal. Aldosterone baseline values were high (1217pmol/L), renin values were low (renin 5.1pg/mL), leading to a high baseline aldosterone to renin ratio (ARR): 132. Overnight dexamethasone test (2mg) was strongly suspicious for autonomous cortisol secretion (cortisol: 62.2nmol/L radioimmunoassay (RIA) {10-60nmol/L} and ACTH <5pg/mL). Due to chronic elevated blood pressure, renin-angiotensin- aldosterone axis test was not performed, as it would be dangerous to discontinue anti-hypertension drug therapy. However, PH was considered, based on the combination of adrenal glands adenomas, severe hypertension with hypokalemia, high aldosterone levels and high aldosterone-renin (ARR) ratio. In order to discriminate adrenal adenoma from hyperplasia, NP-59 scintigraphy was performed under the following technique: To protect thyroid gland against iodine-131 (^{131}I) radioactivity, the patient was encouraged for oral administration of lugol solution (3x3 drops daily) 2 days before, up to 7 days after the radiopharmaceutical i.v. injection. As it was unable to control blood pressure, scintigraphy was carried out without discontinuation or modification of high spironolactone dose (200 mg/day). A dexamethasone-suppression protocol was implemented (4mg/day divided in 4 doses, beginning 7 days before i.v. injection) as inhibition of ACTH secretion is crucial for best imaging discrimination between adenoma and hyperplasia in case of PH. Thirty seven MBq (1mCi) of NP-59, were slowly (over 30sec) injected i.v. One day before imaging, the patient was told to empty the colon using a mild laxative, in order to avoid overlapping bowel activity. A dual head gamma camera equipped with high energy, parallel-hole collimator was used, and imaging (80KeV window centered around 364KeV) was carried out at 48h, 72h and 6 days p.i. (whole body, anterior/posterior abdomen planar of 50,000 counts) (Figure 2) and single photon emission computed tomography (SPECT) acquisition - step and shoot protocol, 2° orbit, 20sec/step, filter-back projection analysis. Because of bowel activity, relative low count rate and high energy photon of ^{131}I, SPECT summed images - by two - as well as cine-mode display were helpful for better visualization) (Figure 3). Prominent left adenoma was revealed, confirming left side aldosterinoma scintigraphic diagnosis. Late Imaging at 6th day was normal - as (often) expected (Figure 4).

According to scintigraphic findings and due to persistent hypertension, successful left adrenalectomy was carried out and biopsy revealed a typical adenoma (Figure 5). Two days later, blood pressure (130/80 mmHg) and serum K^+ (4.0mEq/L) returned to normal values.

Discussion

Although CT is a sensitive imaging modality in detecting adenomas, its sensitivity for bilateral hyperplasia is quite limited. Scintigraphy as a functional, non-invasive, and potentially

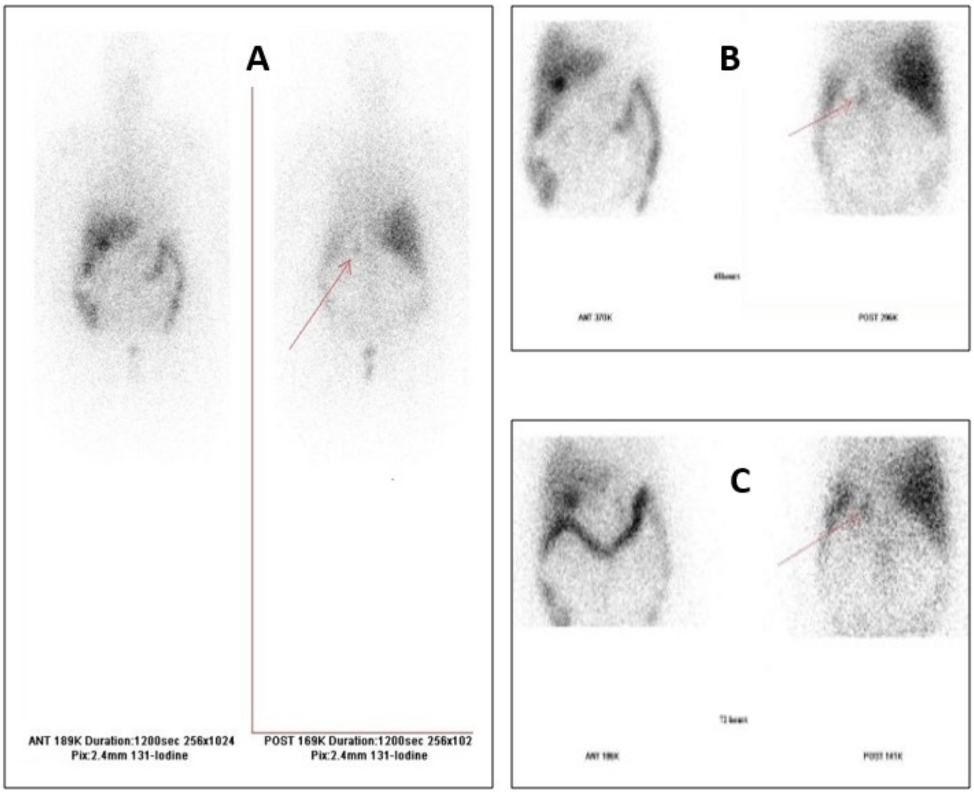

Figure 2. Whole body scintigraphy at 48h: Imaging of left adrenal cortex, at posterior view (arrow). Notice the intense hepatic uptake, the hot spot sign (gallbladder) at the Anterior view and the diffuse presence of radiopharmaceutical into the bowel (normal bio-distribution and enterohepatic excretion) (A). Planar acquisition at 48h (B) and 72 h (C): Left adrenal cortex best seen at posterior view (arrow).

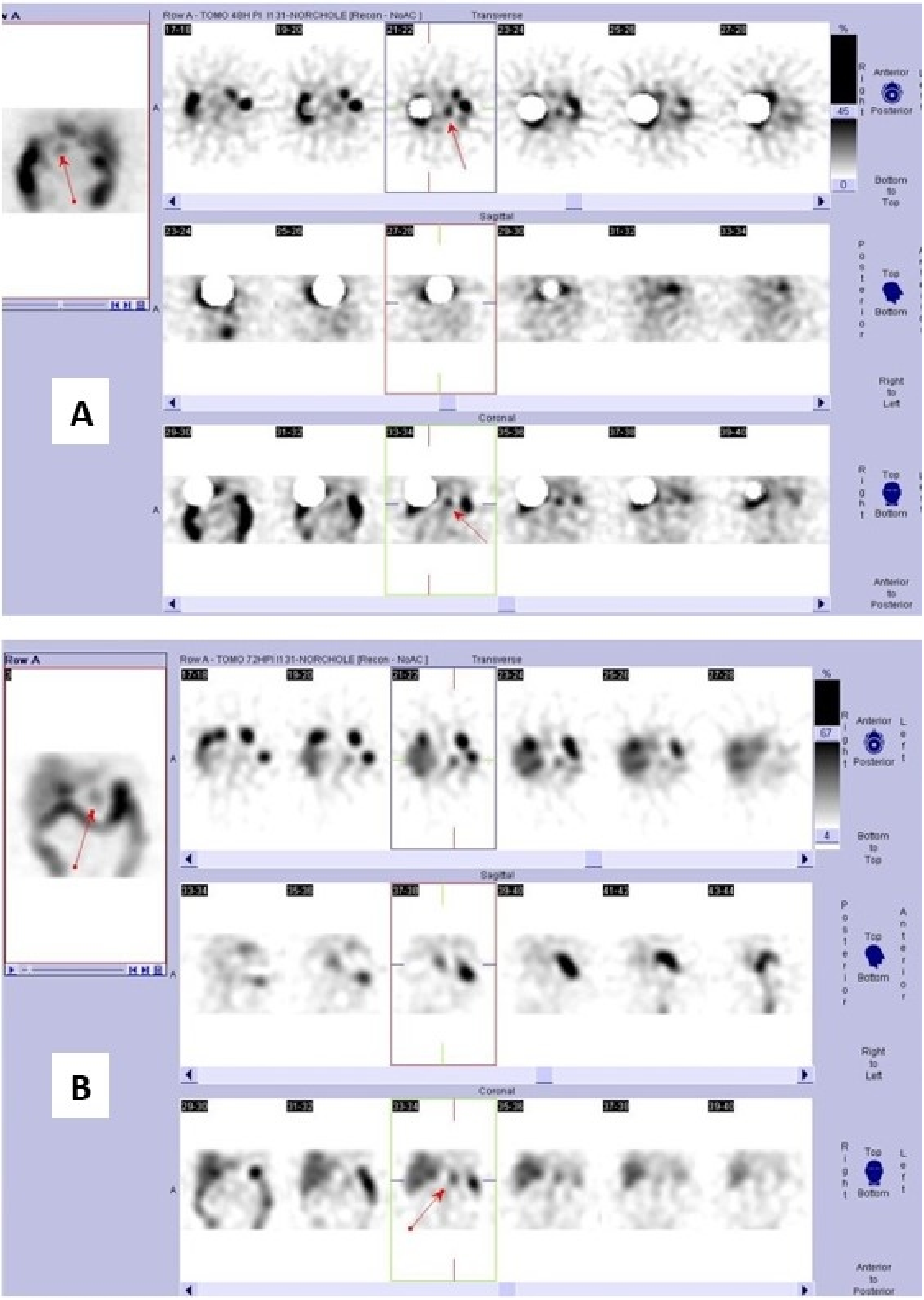

Figure 3. Single photon emission computed tomography at 48h (A): At transverse and coronal slices as well as at cine-mode snapshot (left outer image) the pointed hot spot sign (arrow) represents the visualized left adrenal cortex (adenoma). In order to enhance the contrast, partial masking of liver has been applied. Single photon emission computed tomography at 72h (B): At coronal slices as well as at cine-mode snapshot (left outer image), the pointed hot spot sign (arrow) represents the visualized left adrenal cortex (adenoma). Notice that gallbladder still remains visible, but comparing to SPECT imaging at 48h, left adrenal cortex (adenoma) is better seen, because of more fainted hepatic background. This justifies the value of late imaging, as well as that of SPECT acquisition in order to have an optimum imaging result (without underlying background, and/or normal overlapping structures – e.g. gallbladder).

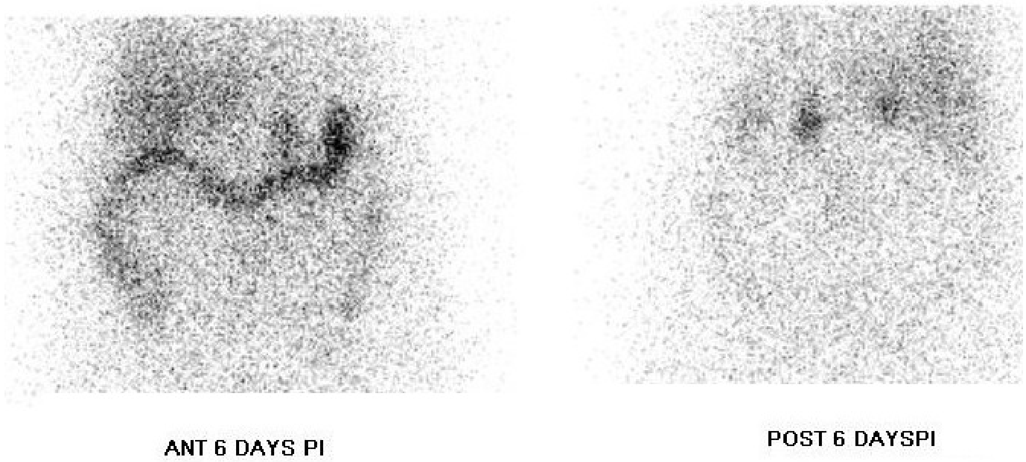

Figure 4. Planar imaging at 6th day: Bilateral visualisation of both adrenal glands (better seen on posterior image). After 5th day p.i. this is a normal finding (see Discussion). For PH under dexamethasone suppression, scintigraphic findings between 48h and 5th day confirm or not the presence of adenoma or hyperplasia.

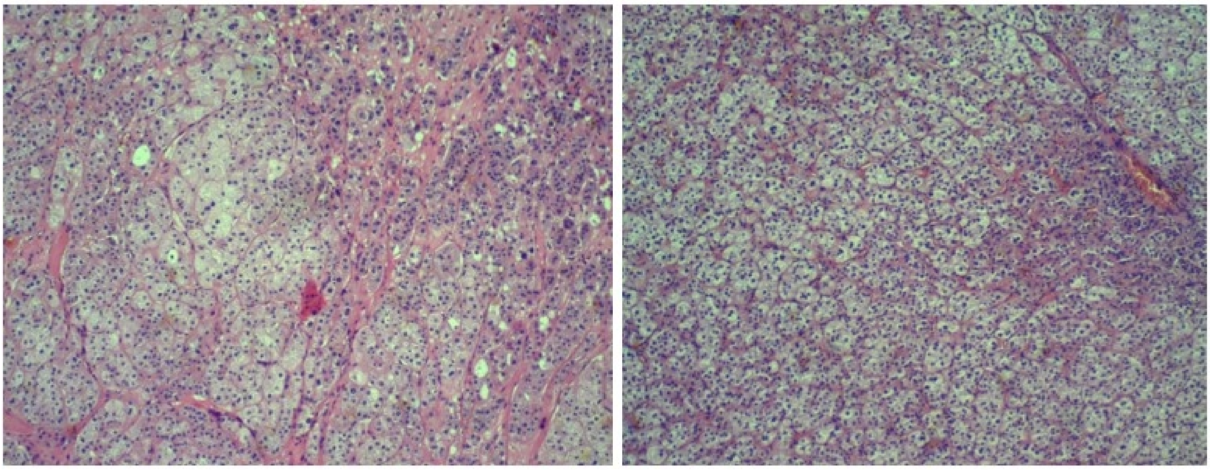

Figure 5. Microscopic appearance of adrenal adenoma hematoxylin/eosin staining (x50).

quantifiable method for adrenocortical imaging, is a safe and accurate imaging procedure for discrimination between adenoma and hyperplasia in case of PH [1-3]. Histologically, adrenal cortex consists of three distinct layers (zones): the outer or glomerulosa zone (for mineralocorticoid production, mainly aldosterone), the middle or fasciculata zone (for glucocorticoid production, mainly cortisol) and the inner or reticulata zone (for sex hormone production). Aldosterone biosynthesis is mediated by renin-angiotensin-aldosterone axis, and cholesterol (normally derived from low-density-lipoproteins - LDL) is the substrate for the above synthesis. The aforementioned biochemical pathway justifies the use of radiolabeled Cholesterol-analogues in order to depict adrenal cortex. So far, three radiopharmaceuticals have been widely used for adrenocortical scintigraphy: ^{131}I-19-iodocholesterol, ^{131}I-6-β-iodomethyl-norcholesterol (NP-59), and ^{75}Se-6-β-selenomethyl- norcholesterol. NP-59 has greater affinity (x5) for adrenocortical uptake, greater in vivo stability, less deiodination with diminished thyroid uptake of free ^{131}I than ^{131}I-19-iodocholesterol [4-7] and a relative lower absorbed radiation dose/injected mCi to adrenal cortex than the other two agents [3, 8]. Radiolabeled cholesterol-analogues are incorporated in LDL, enter adrenocortical cells, where esterification, (as it happens with native cholesterol) takes place, but are not further metabolized. Taken up by liver LDL receptors, these analogues are excreted to bile acid and subject enterohepatic circulation, leading to an increased background colonic radioactivity. To avoid overlapping activity, the use of a soft laxative is recommended one day before examination [4, 7, 8]. In case of PH, oral administration of dexamethasone suppresses the ACTH-dependent component of NP-59 uptake in the (middle) fasciculata zone, facilitating its uptake in the outer cortex layer, and hence, offering an accurate visualization of glomerulosa zone. Early unilateral adrenal visualization (before 5th day) suggests presence of a solidary adenoma, whereas early bilateral visualization (before 5th day) suggests bilateral hyperplasia. Late (after 5th day) adrenal visualization is a normal finding, although the same pattern has been found in some unusual cases of dexamethasone-suppressible hyperaldosteronism [4]. This advantage of NP-scintigraphy (compared to 75Se-6-β-selenomethyl - norcholesterol with longer half-life and hence possible later imaging pathologic findings -up to14 days) findings, makes NP-59 the agent choice for most nuclear medicine departments.

In our case, unilateral imaging of left adrenal adenoma was visualised early (3th and 4th day) whereas (as usually expected) at late imaging (6th day), both adrenals were well and equally depicted [10]. Before scintigraphy, patient preparation must take into account thyroid protection against ^{131}I, as well as factors that may deteriorate the final imaging result, interfering either with the axis (hypothalamic - pituitary -adrenal/renin-angiotensin-aldosterone) or with high cholesterol levels (unwanted competition with NP-59). So far, guidelines strongly suggest blockage of thyroid with potassium perchlorate and discontinuance of certain agents (e.g. spironolactone, ketoconazole, diuretics, oral contraceptives, etc.) in order to achieve optimum NP-59 uptake [1]. If any of the above agents (e.g. spironolactone) are essential for blood pressure control, then the discontinuation decision is up to the clinician team and Scintigraphy can be carried out with potentially reduced sensitivity. Chia-Hui Chang et al. (2018) studied a cohort of 34 patients with PH without discontinuation or modification of antihypertensive medication, and concluded that NP-59 scintigraphy provide safe and accurate lateralization of the lesion [9]. Following the same method, NP-59 scintigraphy of the presented case was done under spironolactone treatment (as it was crucial for blood pressure control) and the final result (unilateral intense imaging), not only justified our choice, but also served as a hallmark for left adrenal gland surgical removal, leading impressively to blood pressure improvement. In conclusion, NP-59 adrenal cortex scintigraphy, remains a reliable and useful tool in depicting adenomas in case of PH, without the need of spironolactone cessation.

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