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Primary Aldosteronism with Bilateral Adrenal Adenomas

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Summary. An unusual case of primary aldosteronism with bilateral single adenomas is reported. The two tumors were revealed by computerized axial tomography and subsequently confirmed by surgical exploration. Spironolactone therapy prior to the operation induced the formation of spironolactone bodies in only one of the two adenomas. As it has been postulated that these cytoplasmic inclusions may reflect the activity of the adenomatous cells, the presence of the bodies in a single adenoma would indicate a unilateral source of the hyperaldosteronism. Thus, the existence of spironolactone bodies could corroborate the data of functional localizing tests more closely than the morphological findings of computerized tomography.

Key words: Primary aldosteronism – Computerized tomography – Adrenal cortex neoplasms – Spironolactone.

Introduction

In primary aldosteronism, elucidation of adrenal anatomy is crucial in deciding between surgical or medical treatment since adenoma responds to surgery better than hyperplasia. Several diagnostic techniques have been described, including adrenal selective venography, adrenal venous aldosterone levels, iodocholesterol scintigraphy, ultrasonography and dynamic hormonal studies (Ferris et al. 1978).

Computerized axial tomography (CAT) has improved the resolution of the adrenals (Brownlie et al. 1978), and alone can demonstrate these glands in an axial plane. Recently it has been useful in the detection of aldosterone-producing adenomas (Karstaedt et al. 1978; Dunnick et al. 1979; Ganguly et al. 1979; Prosser et al. 1979; Linde et al. 1979).

We report here a case of primary aldosteronism, in which bilateral solitary adenomas were revealed by CAT and subsequently confirmed at operation.

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Surprisingly treatment with spironolactone prior to surgery led to the formation of spironolactone bodies in only one of the two adenomas, suggesting a functional difference between both sides.

Clinical History

This 68 year-old white female had been hypertensive for 20 years. She complained of weakness, paresthesiae and tetany. On admission she had a blood pressure of 260/140 mm Hg and grade III retinopathy. Plasma Na was 144, K 1.7, Cl 94 and CO_2 31 mmol/l. Urinary Na was 85 and K 82 mmol/24 h. Plasma renin activity (PRA) was suppressed at 0.04 ng/ml/h and could not be stimulated by standing or furosemide. Aldosterone excretion rate (AER) was mildly increased at 53.3 nmol/24 h (19.2 μg) but inappropriate for the low PRA. Aldosterone secretion rate (ASR) was elevated at 1942 nmol/24 h (699 μg). Plasma aldosterone (PA) decreased after saline infusion from 2.2 nmol/l (77.9 ng/dl) to 0.7 (24.4), but remained too high and revealed diurnal variation, falling from 1.1 nmol/l (39.1 ng/dl) at 8 AM supine to 0.7 (25.3) at 12 M upright and 6 PM upright. The presence of a diurnal rythm was interpreted as being in favor of an adenomatous type of primary aldosteronism.

Adrenal venography and ultrasonography showed no abnormality. The left adrenal vein was easily catheterized and gave a PA:cortisol ratio of 14×10^{-3}, whereas on the right side only the renal vein could be sampled, giving a ratio of 6×10^{-3}.

CAT was performed using a fan-beam rotary scanner (Somaton) with a 4.5 sec scan time and a 4 mm slice thickness. The scan revealed a smooth nodule, 17 mm in diameter, in the lower part of the right adrenal gland (Fig. 1a) and another small rounded mass, 11 mm in diameter, in the upper pole of the left adrenal (Fig. 1b). The remainder of both glands appeared normal. After contrast injection, densitometric changes were in favor of highly vascular bilateral tumors rather than hyperplasia.

Adrenal scintigraphy using ^{131}I-19-iodocholesterol without dexamethasone preparation demonstrated bilateral uptake on the second day, but left-sided predominance on the tenth day (Fig. 2).

Prior to surgery, the patient was given spironolactone 300 mg daily for 8 weeks. During the course of treatment, blood pressure and serum K were normalized, whereas AER was unchanged, at 42 nmol/24 h (15 μg) by the eighth week. ASR fell to 1,256 nmol/24 h (452 μg) by the end of the first week and 1428 nmol/24 h (514 μg) by the eighth week of treatment, still in excess of the normal range.

Surgical exploration by bilateral posterior approach disclosed two solitary adenomas at the sites indicated by CAT. Post-operative blood pressure remained normal without other treatment. AER was below 6.9 nmol/24 h (2.5 μg) and PA below 0.1 nmol/l (5 ng/dl), while PRA was no longer suppressed (0.85 ng/ml/h). A post-operative CAT-scan was uninterpretable due to the presence of numerous surgical clips.

Pathological Findings

Gross Findings

The tumor removed from the right adrenal gland weighed 3.1 g and measured 2 cm in diameter. It was well delimited, golden-yellow in color. On the left side, the specimen consisted of a portion of adrenal gland weighing 1.9 g, which contained a red-brownish encapsulated nodule of 1.3 cm in diameter.

Histological Findings

On the right side, there was an encapsulated adenoma exclusively formed by cells with abundant pale eosinophilic cytoplasm (Fig. 3); these cells were ar-

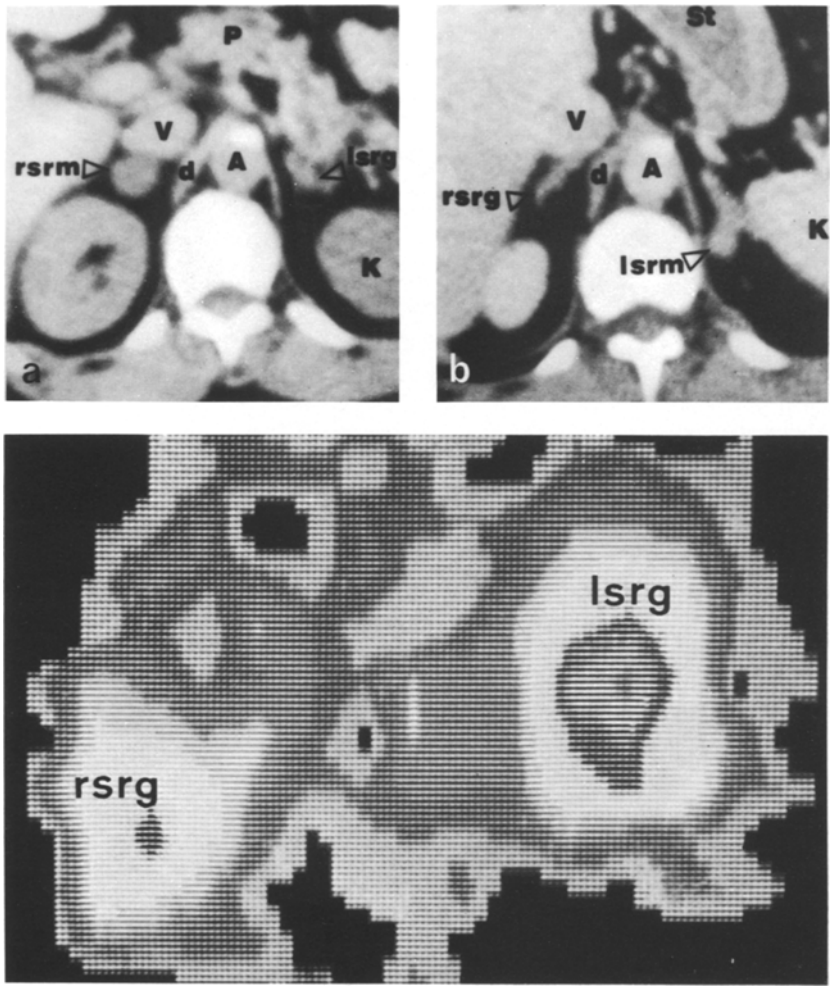
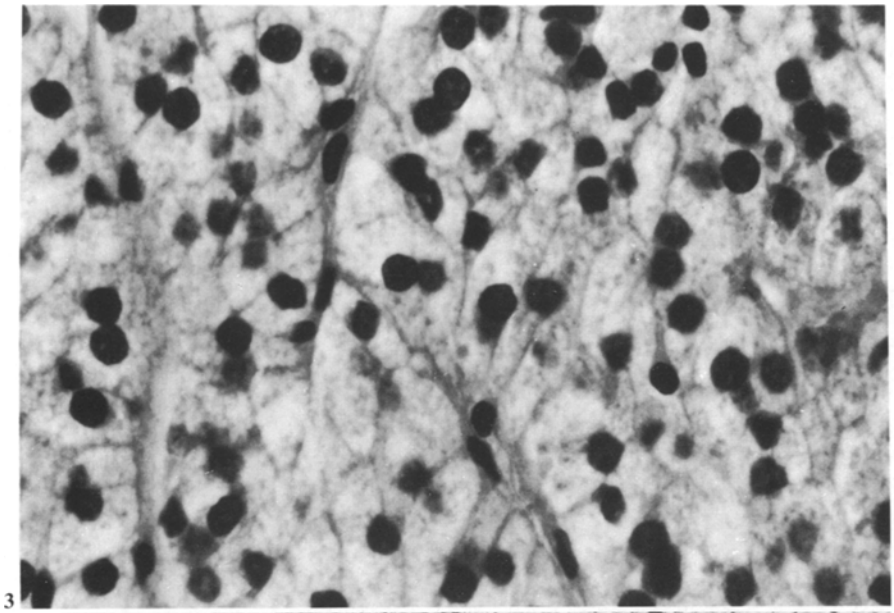


Fig. 1 a and b. Computerized tomogram. **a** Pre-contrast scan at the level of the right adrenal lower pole showing a right supra-renal mass (*rsrm*) behind the inferior vena cava (*V*). **b** Post-contrast scan at the level of the left adrenal upper pole showing a left supra-renal nodule (*lsrm*). Note the normal aspect of the remainder of the right and left adrenal glands (*rsrg, lsrg*). *K:* kidney, *A:* aorta, *d:* diaphragm, *P:* pancreas, *St:* stomach

Fig. 2. Adrenal ^{131}I-iodocholesterol scan on the 10th day revealing bilateral uptake with predominance in the left adrenal gland (*lsrg*)

ranged in clusters and cords separated by delicate vascular septa. No intracytoplasmic inclusion was observed. The nodule from the left side was an adenoma with pleiomorphic appearance. Large zones of eosinophilic cells of glomerular type alternated with foci of foamy clear cells and lobules of adipocytes (Fig. 5). Abundant lipofucsin pigment in these foamy clear cells was responsible for the brownish color of the nodule. Numerous eosinophilic laminated inclusion bodies were noted within the cytoplasm of eosinophilic cells. Generally there



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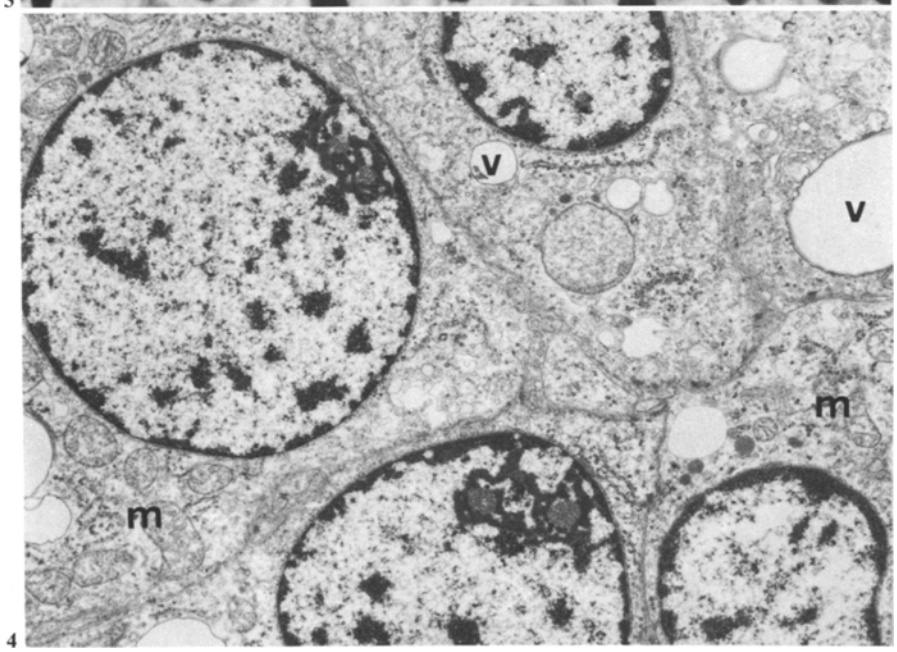

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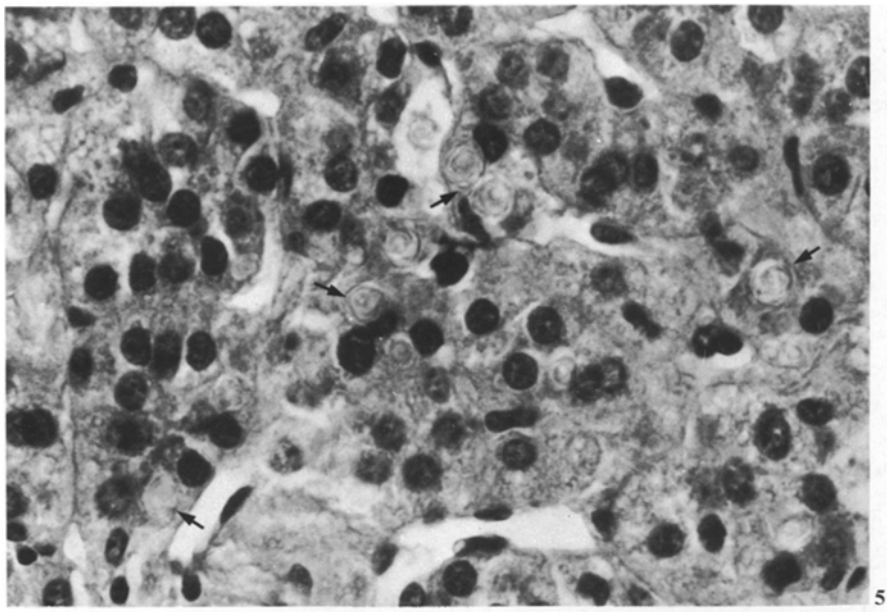
Fig. 3. On the right side, clusters and cords of pale tumor cells are surrounded by delicate vascular septa (HE, $\times 1{,}200$)

Fig. 4. Polyhedral tumor cells of the adenoma from the right side with numerous irregular mitochondria of the tubulo-vesicular type (*m*) and some lipid vacuoles (*v*) ($\times 8{,}600$)



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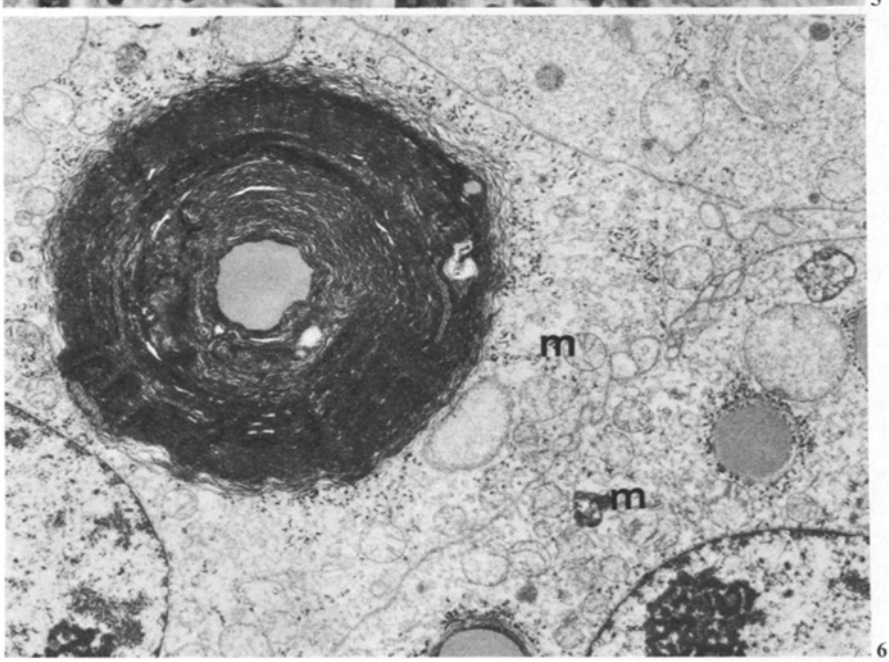

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Fig. 5. On the left side, a large zone of eosinophilic tumor cells containing numerous laminated inclusions, some of them marked by arrows (HE, ×1,200)

Fig. 6. The most frequent tumor cells in the adenoma from the left side were of the glomerular type. They often exhibited spironolactone bodies characterized by layers of double membrane arranged concentrically around a lipid core. Mitochondria (*m*) were generally of the lamellar type (×8,600)

was only one inclusion per cell. Study of the small part of the left adrenal gland removed with the adenoma showed slightly diffuse hyperplasia of the zona glomerulosa without any cytoplasmic inclusion; zonae fascicularis and reticularis appeared normal.

Ultrastructural Findings

Tissue for electron microscopy was fixed in 2.5% cacodylate buffered glutaraldehyde, post-fixed in 10% osmium tetroxide, dehydrated in ethanol and embedded in Epon epoxy resin. Ultrathin sections were stained with uranyl acetate and lead, and studied with a Philips 300 electron microscope.

There was a striking difference between the two adenomas. On the right side, the tumor was formed by irregular polygonal hybrid cells, containing regular, rounded or oval nuclei (Fig. 4). Chromatin was condensed at the periphery of the nucleus. Cytoplasm contained numerous electron-lucent lipid vacuoles of different sizes. The amount of granular and smooth endoplasmic reticulum varied from cell to cell, but these structures were generally not prominent. Mitochondria were numerous, irregular in size and shape, of the tubulo-vesicular type. No spironolactone bodies were seen.

The adenoma from the left adrenal exhibited great variety between different fields. The cells most frequently observed were of the glomerular type, polyhedral, slightly irregular in shape and size. Their nuclei were round or oval with a prominent nucleolus. The agranular endoplasmic reticulum was abundant. The mitochondria were relatively numerous, spherical or oval, essentially of the lamellar type. The granular endoplasmic reticulum was not well developed. A large number of spironolactone bodies, similar to those reported in other studies (Janigan 1963; Conn et al. 1977; Kano et al. 1979), were observed (Fig. 6). The size of these structures varied from 2 to 10 mμ in diameter. They consisted of a central lipid core surrounded by layers of double membranes which were arranged concentrically. Sometimes clusters of vesicules were inserted between these concentric membranes. At the periphery, a continuity between these bodies and the granular endoplasmic reticulum was often noted.

Discussion

Compared with the various techniques used in the identification of aldosterone-producing adenomas (Ferris et al. 1978), CAT may be more promising, as the studies carried out so far show higher accuracy (Karstaedt et al. 1978; Dunnick et al. 1979; Prosser et al. 1979; Linde et al. 1979; Ganguly et al. 1979). However the small size of most adenomas requires high resolution and explains some false negative findings. CAT cannot usually distinguish bilateral hyperplasia from normal glands (Dunnick et al. 1979). Our case illustrates another successful application of this imaging technique, as bilateral adenomas were readily recognized by CAT after negative venography and inconclusive adrenal vein sampling.

Findings were consistent with the iodocholesterol scan, although this latter did not help to separate bilateral adenomas from hyperplasia.

From post-mortem studies the incidence of adrenal nodules varies from 2.9% to 3.6% in the general population, and up to 20% in hypertensive patients (Symington 1969). It should not therefore be uncommon to detect non-functioning adrenal nodules by CAT. Yet the true incidence of functioning multiple and bilateral aldosterone-producing adenomas is unknown, since most cases are operated on only on one side. In a recent series (Linde et al. 1979), CAT identified two cases of bilateral tumors, while other localizing tests pointed to a single side as the origin of hyperaldosteronism. Neither patient had evidence of aldosterone excess after unilateral adrenalectomy, suggesting that the contralateral tumor was not functioning. Therefore a cautious attitude should be adopted as CAT may reveal a number of adenomas, possibly inactive, which should be left untouched.

As our patient received spironolactone pre-operatively for 8 weeks, formation of spironolactone bodies could be expected in the two adenomas and it was surprising to find them only on the left. The high level of plasma aldosterone in the adrenal vein, the predominant ^{131}I-iodocholesterol uptake and the electron microscopic appearances of the adenomatous cells all suggest a high degree of endocrine activity of the left-sided tumor, responsible for the clinical manifestations of hyperaldosteronism. No blood was sampled on the right side, but from other results it can be postulated that the right adenoma was less active, or even inactive. Since it has been claimed that spironolactone bodies are found only in active cells (Conn and Hinermann 1977), their presence in the left adenoma may only point to another feature of endocrine activity. Tissue measurement of aldosterone could have helped in the evaluation of endocrine function and proved that spironolactone bodies can be used as another marker of excessive steroidogenesis.

The pathogenesis of the characteristic cytoplasmic inclusions produced by spironolactone and univocally found in the glomerular cells is yet to be elucidated (Kano et al. 1979). Conn and Hinermann hypothesized that spironolactone bodies are a morphological expression of an enzymatic block in aldosterone biosynthesis: their increased frequency seems to follow the diminution of aldosterone excretion rate during the first weeks of treatment; they tend then to disappear although this finding has not been accredited by others. However, as the enzymatic steps of steroidogenesis take place in mitochondria and microsomes, spironolactone bodies, reflecting a reaction in the endoplasmic reticulum, may indicate an effect of drug metabolism rather than a biosynthetic block. It is not known how specific this type of cytoplasmic inclusion could be with respect to drug therapy. In the present case, spironolactone administration induced only slight decrease in aldosterone secretion rate which, from our experience in primary aldosteronism (unpublished data), may have been due to day-to-day fluctuation rather than to some enzymatic block. Indeed, in other conditions of spironolactone therapy, we have been unable to demonstrate any clear-cut inhibitory effect (Gaillard et al. 1980).

In conclusion, this unusual case of bilateral adrenal adenomas emphasizes the value of CAT as a non-invasive and reliable method of morphological

identification. However, since its interpretation may be misleading as far as the endocrine activity is concerned, histological search for spironolactone bodies can give better insight into adenoma hormonal function and may more closely reflect the findings of other non-morphological adrenal localizing techniques.

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