REVIEW

Aldosterone- and cortisol-co-secreting adrenal tumors: the lost subtype of primary aldosteronism

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Abstract

Current guidelines suggest proving angiotensin-independent aldosterone secretion in patients with primary aldosteronism (PA). It is further recommended to demonstrate unilateral disease because of its consequence for therapy. A general screening for excess secretion of other hormones is not recommended. However, clinically relevant autonomous aldosterone production rarely originates in adrenal tumors, compromised of *zona glomerulosa* cells only. This article reviews published data on aldosterone- and cortisol-co-secreting tumors and shows that pre-operative diagnosis of such a lesion is beneficial for patients. Overt or subclinical glucocorticoid hypersecretion may interfere with diagnostic studies, e.g. adrenal venous sampling, screening of familial forms of PA on the basis of serum 18-hydroxy-cortisol (18-OH-F) determination, and provoke glucocorticoid deficiency after surgical removal of the tumor. In addition, knowledge from histological and molecular studies in patients with aldosterone- and cortisol-co-secreting tumors challenges some concepts of the development of adrenal autonomy. The presence of an aldosterone- and cortisol-co-secreting adrenocortical tumor should be considered if a patient has i) PA and an adenoma that is larger than 2.5 cm, ii) cortisol that is non-suppressible with overnight low-dose dexamethasone, or iii) grossly elevated serum levels of hybrid steroids, such as 18-OH-F.

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Introduction

Conn described primary aldosteronism (PA) as a syndrome of hypertension, sodium retention, and hypokalemic alkalosis that could be cured by removal of an adrenal cortical tumor and provoked by infusion of aldosterone (1). Later, PA was recognized to occur as a result of a heterogeneous group of disorders, including aldosterone-producing adenomas (APA), idiopathic uni- or bilateral adrenal hyperplasia, adrenocortical carcinoma (ACC), aldosterone-producing tumors of the ovary, or from inherited forms of familial hyperaldosteronism (FHA), types 1–3 (2–6).

To meet the clinical challenges adequately, a clinical practice guideline for the management of patients with suspected PA was developed recommending an algorithm for screening, confirmatory, and subtype testing (7). However, a number of open questions remain and a controversial debate arose on the quality of diagnostic tests that we employ for our patients today (8–11). In addition, there is one subtype of PA that is under-recognized in current reviews and guidelines and that seems worthy of more detailed discussion. This is because patients with the entity of a cortisol-co-secreting type of APA (aldosterone- and cortisol-producing

adenoma (A/CPA)) may present with additional clinical features, impacting on care after tumor resection and because routine diagnostic tests may become more difficult to interpret and will have to be complemented.

Methods

In this review, we focus on 35 patients with A/CPA reported to date, including ours (12–37) and 24 patients with ACC who were documented to have both PA and hypercortisolism (aldosterone- and cortisol-co-secreting ACC (A/C-ACC)) (38–57). The reports were selected after using PubMed to search through MEDLINE, employing the following terminologies: ‘adrenal cortisol aldosterone case’, ‘APA cortisol’, ‘CPA aldosterone’, ‘aldosterone cortisol adenoma’, ‘adrenocortical adenoma hormone excess’, ‘adrenal adenoma hormone excess’, ‘adrenal adenoma PA’, and ‘adrenal adenoma PA cushing’. For the identification of articles relevant for A/C-ACC, we replaced the term ‘adenoma’ with ‘carcinoma’ but excluded all articles that reported also androgen excess in addition to excess cortisol and aldosterone secretion. We have also searched the reference sections of relevant articles. Thereby, we also

found another ten articles dealing with A/CPAs written in Japanese that were not included in our analysis because of data interpretation problems (Supplementary Table 1, see section on supplementary data given at the end of this article). Concerning A/CPAs, all other articles could be included for this work. We also report on eight patients with A/C-ACC who have been treated in our institution during the last 10 years and who were selected from the files.

When showing the results of endocrine function tests and thus accepting the limitations in pooling hormonal data, we recomputed the reported data into conventional units, irrespective of assays that were applied, because frequently, they were not described. For upper or lower limits of normal and for calculation of renin concentrations from renin activities, we followed the suggestions of consensus papers and guidelines (7, 58). When a laboratory value was noticed to be high or low, cases were included in percentage analyses for these variables but were not used for extrapolations to calculate means or s.d.

Current knowledge on A/CPA

Clinical presentation of cases with A/CPA

On average, patients with the subtype of an A/CPA were 52 (range 34–80) years old. More than two-thirds of reported patients were female subjects, although preference of female sex in patients with PA is not a consistent observation (59–61).

The vast majority of patients with A/CPA presented with therapy-resistant hypertension, combined with electrolyte disorders (Tables 1 and 2). Interestingly, 14% of patients presented with symptoms typical for hypercortisolism. Clinical signs of Cushing’s syndrome were noted in about 24% of patients at the time of presentation. As much as 74% of cases were reported as having preclinical Cushing’s syndrome or subclinical autonomous glucocorticoid hypersecretion (SAGH; Table 1). Of note, two patients were retrospectively diagnosed with hypercortisolism due to an adrenal crisis after adrenalectomy. These observations show that screening for hypercortisolism is of relevance in patients with an adrenal tumor even if it is associated with PA.

Laboratory data of patients with A/CPA

Work-up of PA There was a high prevalence of hypokalemia (Table 2) that may in part be due to the fact that many of the patients were already diagnosed long before the introduction of the aldosterone to renin ratio (ARR) and its acceptance as a screening tool (62). The mean ARR was 506 when calculated as aldosterone in ng/l divided by renin in ng/l. Confirmatory testing was performed in slightly more than 50% of cases. Endocrine function tests for confirmation included

Table 1 Clinical data of patients with aldosterone- and cortisol-co-secreting adrenocortical tumors available from the literature A/CPA_{all pts} and A/C-ACC_{literature} and own files A/CPA_{all pts} and A/C-ACC_{own pts}.

	A/CPA _{all pts}	A/C-ACC _{literature}	A/C-ACC _{own pts}
No. of cases	35	24	8
Age (years)	51.6 ± 10.6	44.3 ± 19.6	54.0 ± 15.4
Female (%)	72.7	52.4	75.0
Tumor size (mm)	26.2 ± 10.0	110 ± 88	100 ± 26
Cortisol excess screening (%)	94.3	91.7	87.5
Confirmation test performed (%)	90.9	90.5	85.7
Cushing’s syndrome noticed (%)	27.3	83.3	87.5
Aldosterone excess screening (%)	100.0	100.0	100.0
Confirmation test performed (%)	51.4	60.9	62.5
Hypertension (%)	87.9	100.0	87.5

A/C-ACC, aldosterone- and cortisol-co-secreting adrenocortical cancer; A/CPA, aldosterone- and cortisol-producing adenoma; pts., patients.

saline loading (4×), assessment of aldosterone before and after fludrocortisone (4×) or captopril (10×), upright posture (14×), and determination of urinary aldosterone (metabolite) excretion (12×). While saline loading rendered clear abnormal results in only 60% of cases, suppression with fludrocortisone proved autonomous aldosterone secretion in 100%. Captopril testing was performed in 28.6% of patients and showed an insufficient increase in renin activity in 80% of patients and an insufficient decline in aldosterone in 100% of cases. The upright-posture tests showed no increase in renin values in 84.6% of cases and an increase in plasma aldosterone in 38.5% of patients. In three cases (8.6%), a decrease in plasma aldosterone was observed after 4 h of standing and walking. Abnormal secretion of aldosterone or its metabolites was found in 37% of patients with A/CPA (please, see Table 2).

Work-up of hypercortisolism Given the low rate of use of confirmatory testing for PA, there was a relative high proportion of patients in whom dexamethasone suppression tests were performed (32×). Abnormal results of suppressed cortisol values were reported in 90.6% of patients. Other tests to characterize hypercortisolism included stimulation with corticotropin-releasing hormone (CRH) (12×), desmopressin (1×), or ACTH (7×). Measurement of urinary-free cortisol was performed in 17% of patients, determination of urinary excretion of 17-ketosteroids and/or 17-hydroxycorticosteroids in 42.9% of patients with some overlaps. In addition, low plasma ACTH values were seen in 55.9% of patients, and DHEA-S levels were analyzed in 57.1% showing decreased synthesis in 35% of investigated patients. CRH testing showed an insufficient increase in ACTH concentrations in about 40% and an insufficient increase in cortisol concentrations in about 70% of studied patients. ACTH testing revealed a normal response of both cortisol and aldosterone in each case and inconsistent results in the increase of 17-hydroxy-progesterone.

Table 2 Laboratory data and endocrine function tests of patients with aldosterone- and cortisol-co-secreting adrenocortical tumors available from the literature A/CPA_{all pts} and A/C-ACC_{literature} and our own files A/CPA_{all pts} and A/C-ACC_{own pts}.

	A/CPA _{all pts}	A/C-ACC _{literature}	A/C-ACC _{own pts}
Hypokalemia (%)	81.8	91.7	87.5
Serum potassium (mmol/l)	3.1 ± 0.8	2.5 ± 0.9	3.3 ± 0.8
Plasma aldosterone (ng/l)	414.6 ± 429.5	694.3 ± 504.3	381.2 ± 277.1
Renin (ng/l)	2.1 ± 2.7	2.9 ± 5.2	2.3 ± 1.3
ARR in (ng/l:ng/l)	506.2 ± 629.5	773.2 ± 912.1	611.1 ± 264.8
ARR abnormal (%)	90.9	100.0	62.5
Basal cortisol (μg/dl)	14.7 ± 5.5	16.9 ± 6.4	36.7 ± 13.7
Cortisol after low-dose dexamethasone ^a	10.0 ± 7.9	3.7 ± 0.6	28.4 ± 24.2
Cortisol after high-dose dexamethasone ^b	7.9 ± 8.2	–	–

A/C-ACC, aldosterone- and cortisol-co-secreting adrenocortical cancer; A/CPA, aldosterone- and cortisol-producing adenoma; pts., patients.

^aRefers to the dexamethasone suppression test that is done overnight or over an interval of 2 days with a maximal dose of 3 mg.

^bRefers to the dexamethasone suppression test that is done with 4 mg or higher.

Work-up of co-secretion of aldosterone and cortisol

Co-secretion of aldosterone and cortisol has been described in APA and in ACTH-independent macronodular adrenal hyperplasia (63). APAs can be distinguished by their size, cell types, hormone over-secretion, and responsiveness to angiotensin 2. In addition, *in vitro* molecular and immunohistochemistry studies as well as clinical studies with infusion of various compounds *in vivo* showed that in patients with APA, aldosterone secretion may be regulated also by multiple other factors, mainly arginine, vasopressin, and serotonin (64). However, they can also be differentiated by the extent of hormone suppression by dexamethasone and by the secretion of hybrid steroids, as 18-hydroxy-cortisol (18-OH-F) (65–67). In 'ordinary' APAs, mild secretion of hybrid steroids can occur, and normal zona glomerulosa cells have the potential to metabolize secreted cortisol to 18-OH-F (7, 68). Furthermore, tissue derived from APAs actively converts deoxycorticosterone and 18-hydroxy-11-deoxycorticosterone to 18-hydroxycorticosterone and aldosterone respectively, and APA tissue can metabolize aldosterone and cortisol precursor steroids to cortisol (69). Thus, elevated levels of 18-OH-F may solely be the consequence of very active steroidogenesis in adrenal tumors.

However, high levels of 18-OH-F are also a typical finding in patients with FHA type 1 and type 3. FHA-1 and 3 are rare subtypes of PA. FHA-1 is caused by an unequal crossing over between the 11β-hydroxylase (*CYP11B1*) and aldosterone synthase (*CYP11B2*)

genes resulting in a chimerical *CYP11B1/CYP11B2* gene (5, 70). As a result, aldosterone synthase is also put under the control of ACTH, and the adrenal glands can produce 18-OH-F from 18-hydroxy-corticosterone (18-OH-B) (71). Aldosterone synthesis can therefore be partly suppressed by treatment with dexamethasone that is of diagnostic and therapeutic value. FHA-3 has recently been described (4). The underlying genetic defect, however, has not yet been identified, and the mechanism of hybrid steroid generation is not yet clear. However, hybrid steroids are non-suppressible with dexamethasone.

Of interest, grossly elevated levels of 18-OH-F and 18-OH-B were found in two cases with A/CPA. Here, the *CYP11B1/CYP11B2* hybrid gene was not found, and mutations in the aldosterone synthase gene or a remarkable family history could be excluded (13). Thus, A/CPAs may also oversecrete 'hybrid' steroids such as 18-OH-F, an observation that may be of diagnostic value.

Subtype differentiation and radiological findings in patients with A/CPA

For identification of adrenal tumors, multiple imaging techniques were employed, including computed tomography (CT, 23×), magnetic resonance imaging (MRI, 8×), ultrasound of the abdomen (3×), and body X-ray pyelogramme (1×). Correct tumor localization was seen in 100% of CT scans and in 87.5% of MRI scans. Using these methods, a tumorous lesion was found in 31 out of 34 cases (91%), while in one case with unilateral disease, no data were shown (36). A solitary single adenoma was found in 29 patients (85.3%), whereas multiple lesions were seen in five cases (14.3%). In three of these five patients (60%), bilateral abnormalities were found.

Interestingly, the averaged diameter of the A/CPA lesions was 26.2 mm, while for APA, it is reported to be around 15 mm (7, 14, 72). This difference in size may explain why cortisol co-secretion may become detectable. APAs that solely consist of zona glomerulosa cells are very rare and usually, APAs are composed of different cell types (73–75). Thus, APAs seem to have the potential of excess co-secretion of both aldosterone and cortisol (13, 76). Hence, in A/CPAs, the co-secretion of cortisol may become apparent for three different reasons. First, A/CPAs could have a higher proportion of cortisol-producing cells than adrenocortical tumors, which have been recognized as pure APAs. Secondly, the quantity of cortisol-producing cells may become clinically detectable because the tumor is large enough to secrete relevant amounts of glucocorticoids, although the proportion of cortisol-secreting cells within the tumor may remain similar as in APAs (Fig. 1). Thirdly, tumors larger than 2 cm in diameter may lead to a diagnostic bias because an atypical size may prompt further diagnostic work-up. Alertness and

application of adequate endocrine function tests more likely reveals excess cortisol co-secretion. Possibly, subclinical hypercortisolism may also be more frequently found in smaller APAs, if it was investigated more often. This would be consistent with *in vitro* studies revealing the capacity of APA cells to produce cortisol (65, 77, 78). Thus, A/CPAs are also interesting from a developmental point of view.

To detect lateralization of aldosterone secretion, adrenal venous sampling (AVS) was performed in ten patients and adrenal nucleotide scintiscan in 19 patients with A/CPA. AVS indicated the correct localization of the hormonally active A/CPA tumor in seven out of ten cases (70%). In two of the three unsuccessful cases, a correct localization was actually reached. However, cortisol co-secretion by the adrenal tumors was not recognized and led to false interpretation. In one report, it is not stated whether the two patients with A/CPA were correctly identified by AVS and the data were not presented.

A likely reason is that correction of aldosterone values for excessively secreted cortisol may yield false-negative aldosterone-to-cortisol ratios at the side of the adenoma and a low cortisol level in the contralateral adrenal vein. This can result in a low selectivity index, as it was shown in one report where adrenalin values proved correct catheter positioning in the adrenal vein (79).

Correct lateralization was achieved in 100% of adrenal scintigraphic studies, while in one case, a repeated scintiscan was necessary to demonstrate the A/CPA lesion and was performed a few years later.

Surgical therapy and post-interventional adrenal crisis

All patients reported underwent adrenalectomy. In two cases, autonomous cortisol co-secretion was not studied before surgical intervention and adrenal crisis developed (14, 21). Although autonomous cortisol co-secretion was known in all other cases

pre-operatively, another six patients, who had been put on substitution therapy with oral glucocorticoids after surgery, experienced severe symptoms of adrenal insufficiency (22, 29, 32, 34). One patient made this experience two times when a reduction in the dose of glucocorticoid was tried. All in all, glucocorticoid substitution was administered in 17 cases only, and adrenal insufficiency was not noticed in 12 of those cases.

Data obtained from in situ and in vitro studies of A/CPA tissues

Histological and immunohistochemical studies The fact that the A/CPA tumors were large (Table 2) in comparison to pure APAs may raise the question whether or not these lesions hold the potential of malignancy. Concerning this point, all resected tumors were examined histologically, and the diagnosis of an adrenal adenoma was confirmed. In five cases, it was definitely stated that there was no evidence for malignancy according to the criteria of Weiss (23, 28, 30, 32, 34, 80). However, the Weiss score was not given as an explicit number in the majority of cases.

Macroscopically, the tumors showed a golden yellow cut surface. Histologically, they exhibited large clear cells and small compact cells. In 37.1% (13 cases), atrophy of the adjacent non-neoplastic tissue was described (12–15, 18, 19, 21, 23, 26–28, 30, 32, 34, 37). Immunohistochemical examination was performed in 57.1% (20 cases) assessing the expression of CYP17A (20×), CYP11B1 (8×), CYP11B2 (2×), side chain cleavage (CYP11A1) (8×), 21-hydroxylase (CYP21A2) (8×), 3β-hydroxysteroid-dehydrogenase (type II) (HSD3B2) (10×), DHEA-ST (9×), melanocortin 2 receptor (MC2R) (2×), and angiotensin II receptor (type I) (AT1R) (2×) (Table 3).

Antibodies against CYP17A showed positive staining in all tumors at least focally (21, 23, 26, 32, 33) in compact cells (21, 23, 26). Also, stainings with antibodies against CYP11A1, CYP21A2, CYP11B1, and CYP11B2 were all positive. Fujii *et al.* (16) precisely described a positive immunoreaction of CYP11B1 predominantly in compact cells and of CYP11B2 mainly in the predominant clear cells. Studies of HSD3B2 expression showed positive results in all analyzed tumorous tissues and negative results in adjacent non-neoplastic tissues (26, 27, 32, 37). In tumorous tissue, DHEA-ST showed positive results in three cases (12, 30, 37) and negative results in six cases (12, 23, 26, 32). Clinical data suggesting excess androgen secretion were not present in the three cases with tissues tested positive for DHEA-ST. In adjacent non-neoplastic tissue, DHEA-ST was tested positive in all cases examined ($n=6$) (23, 26, 27, 30, 32). However, immunoreactivity of DHEA-ST was weak or suppressed in 83.3% ($n=3$) (26, 27, 32).

Figure 1 This sketch illustrates the composition of a cortisol-producing adrenal adenoma (CPA, panel A), an aldosterone-producing adenoma (APA, panel B), and an aldosterone- and cortisol-co-producing adenoma (A/CPA, panel C). It is shown that APAs do rarely consist of zona glomerulosa-derived cells only. However, autonomous secretion of cortisol does not become clinically relevant. If the size of an APA exceeds a certain limit, glucocorticoid oversecretion by the tumor may become apparent or detectable by endocrine function tests. Alternative explanations are given in the text.

Table 3 Review of the immunohistochemical studies in aldosterone- and cortisol-co-secreting adrenocortical adenomas.

References		Cytochrome P450					HSD3B2		DHEA-ST		MC2R	AT1R
		17A	11B1	11B2	11A1	21A2	Tumor	Adjacent	Tumor	Adjacent		
(12)	#1	+					+		+			
	#2	+							—			
	#3	+										
	#4	+							—			
	#5	+					+					
	#6	+					+		—			
	#7	+										
(16)			+ (coc)	+ (clc)								
(21)	#1	+	+		+	+	+					
	#2	+	+		+	+	+					
(23)		+	+		+	+			—	+		
(26)		+						—	—	↓		
(27)		+			+	+		—		↓		
(30)	#1	++ (coc)	+		+	+	+		Weak	Weak		
	#2	+ (clc)	+		+	+	+			Weak		
(32)		Focal	+		+	+		—	—	Weak		
(81)		Focal								Weak		
(34)			+	+			+					
(13)	#1	+									↓	↓
	#2	+									↓	↓
(37)		+	+		+	+	+	—	+	↓		

coc, compact cells; clc, clear cells; +, positive staining; —, negative staining; ↓, decreased expression.

Molecular biological examination The expression of *HSD3B2*, *17α*-hydroxylase (*CYP17A1*), *CYP11B1*, *CYP11B2*, *CYP11A1*, *CYP21A2*, and *DHEA-ST* mRNAs was studied in tumorous and non-neoplastic tissues of four cases using molecular biological methods (21, 28, 33, 37). Northern blot analysis revealed the expression of *CYP11A1*, *CYP17A1*, and *CYP21A2* in both tumorous and non-tumorous tissue (21). Besides, mRNA ratios of *CYP17A* from tumorous and non-tumorous tissues from A/CPA were compared with tissues from APA by densitometry of the blotted bands, CPA, and non-functioning adrenal adenoma. *CYP17A* mRNA showed higher expression in tumorous (TT) than in non-tumorous tissue (NT) from A/CPA, whereas APA showed higher expression in NT than in TT. In non-functioning adrenal adenoma, there was no

expression detected in TT but normal expression in NT. Finally, in CPA, expression of *CYP17A* was detected in TT but not in NT. In another case, multiple bilateral tumors have been detected and analyzed using *in situ* hybridization (ISH) (28). There was one tumor in the right adrenal, one on the left adrenal, and multiple minute nodules in both the glands. Expression of *CYP17A* and *HSD3B2* was found to be strong in the right tumor, while expression of *CYP17A*, *HSD3B2*, and *CYP11B* was normal in the left tumor. *HSD3B2* and *CYP11B* were detected in the minute nodules, and it was found that *HSD3B2* as well as *DHEA-ST* was suppressed in non-neoplastic adjacent tissue. Using real-time PCR (RT-PCR), the ratio of *CYP17A*/*CYP11B2* in A/CPA was determined and compared with ratios in APA, CPA, and a whole normal adrenal gland

Table 4 Review of the molecular studies in aldosterone- and cortisol-co-secreting adrenocortical adenomas.

Methods	Reference	Structure	HSD3B2	Cytochrome P450					DHEA-ST
				11A1	17A	21A2	11B1	11B2	
Northern blot	(21)			+	+	+			
ISH	(28)	Right tumor	++ +		++ +				
		Left tumor	+	+		+	+		
		Nodules	+	—		+	+		
		Adjacent	↓						
RT-PCR	(81)				↑				↓
	(37)	Clear cells Comp. cells						↑ APA-like CPA-like	

APA, aldosterone-producing adenoma; comp., compact; CPA, cortisol-producing adenoma; HSD3B2, 3β-hydroxysteroid-dehydrogenase type 2; ISH, *in situ* hybridization; RT-PCR, quantitative reverse-transcriptase PCR; +, evidence of expression; +++, evidence of strong expression; —, no expression; ↓, decreased expression; ↑, increased expression.

(NAG) (33). The study showed that values obtained in A/CPA (1.9) were between the values obtained in APA (0.9 ± 0.1) and CPA (2.3 ± 0.5) and NAG (2.8). Another RT-PCR study was performed analyzing the ratio of *CYP11B2* mRNA and glyceraldehydes 3-phosphate dehydrogenase in APA and CPA (37). It was distinguished between the tissue consisting mainly of clear cells and that comprised of compact cells. Clear cells showed values similar to CPA, while values of compact cells showed were comparable to APA (Table 4).

Bottom line A lot of studies have been performed, and several different methods have been employed to explore and characterize the tumorous tissues secreting both aldosterone and cortisol. In all cases, the presence of enzymes necessary for steroidogenesis has been demonstrated. Although enzyme activities do not necessarily follow from protein or RNA expression studies, e.g. stainings or PCR, Suzuki *et al.* (81) found that except for an elevated *CYP11B2* activity, the activities of steroidogenic enzymes, including *P450scc*, *CYP11B1*, *CYP11B2*, *CYP17A*, and *CYP21A2*, are conserved in APA tissue and are not very much different from normal controls or adjacent tissue. As already mentioned above, APA tissue can also make cortisol (65, 77, 78).

Patients with A/C-ACC

Published patients with an A/C-ACC were 44 (range 3–79) years old, half of them of female sex. In seven out of 25 case reports, the tumor was classified as ACC according to the criteria of Weiss. In three publications, there was no referral to the criteria of Weiss but the tumor was classified as ACC, e.g. because of metastasis. In the remaining 15 case reports, Weiss criteria, including atypical mitoses, diffuse architecture, necrosis, invasion of tumor capsule, and others, were mentioned as characteristics of the adrenocortical tumor, to be classified as malignant, but the Weiss score was actually not given as a cipher. The Weiss scores of our own patients ranged between 4 and 6, whereby in two cases, no material from the original tumor could be obtained, and the diagnosis was also based on the appearance of metastasis with hormone excess and on the original histopathological reports. As an example, Fig. 2 shows an A/C-ACC with unhomogenous expression of the ACTH receptor.

However, all patients were hypertensive and had hypercortisolism. Low serum/plasma potassium values were also a general finding (Table 1). Plasma ACTH values were determined or communicated only in a minority of patients and not always suppressed. Suppression of cortisol with dexamethasone was impossible even in patients with normal urinary excretion of free cortisol or 17-hydroxycorticosteroids. Diuresis of aldosterone or oxo-steroids were elevated in every person with an A/C-ACC with one exception of a

Figure 2 Section of an adrenocortical carcinoma (Weiss score of 4), which showed a slight excess secretion of both cortisol and aldosterone. Staining to the ACTH receptor was positive in some areas of the tumor (red cells, photograph with 20× magnification).

patient who had an elevated ARR. Interestingly, confirmatory or repeated testing for hypercortisolism was performed more consistently than tests for the diagnosis of hyperaldosteronism despite a high prevalence of hypokalemia. This holds also true for our own patients (Table 1).

At the time of diagnosis, 40% of published patients and 75% of ours had already metastatic disease. Progression or relapse after operation was observed in 80 and 100% of patients respectively. We have no conclusive explanation why our patients were older at the time of presentation (Table 1), had higher cortisol levels, lower ACTH concentrations, and higher urinary excretion rates of free cortisol (755 vs 550 µg/day). Of note, the A/C-ACC phenotype was present in eight of 29 patients with an ACC during the last 10 years. As an adjunct, another 11 patients had an ACC. They were normokalemic and had probably no excess aldosterone secretion. In these patients, however, diagnosis was insufficient to rule out or prove the existence of an A/C-ACC.

Summary

PA is considered to be the most common reason for secondary hypertension (82, 83). Among adrenal disorders that lead to PA, the subtype of aldosterone- and cortisol-co-secreting tumors can be recognized separately. This is because patients with aldosterone- and cortisol-co-secreting adrenal tumors may display unique laboratory features. This may cause unexpected clinical constellations and may even lead to misinterpretation of diagnostic tests, as it was the case in AVS.

Aldosterone- and cortisol-co-secreting tumors can be benign (A/CPA) or malignant (A/C-ACC), of which the

latter was relatively large at the time of presentation. Both entities may present with overt or subclinical hypercortisolism. Therefore, for pre-operative detection of cortisol co-secretion, the low-dose overnight dexamethasone suppression test turned out to be an adequate method. Also, the measurement of hybrid steroids may further lead in the clinical work-up. The finding of an aldosterone- and cortisol-co-secreting tumor also impacts on the therapy and the post-operative management, so that adrenal crises can be circumvented. Using histological and molecular biological methods, the clinical suspicion of cortisol co-secretion by an APA can be confirmed. In addition, a more detailed histological and molecular work-up of such lesions may inform us on additional ways of development of adrenal autonomy.

Supplementary data

This is linked to the online version of the paper at <http://dx.doi.org/10.1530/EJE-10-1070>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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