

# Aldosterone-producing adrenocortical carcinoma: an unusual cause of Conn's syndrome with an ominous clinical course

Teresa M Seccia<sup>1</sup>, Ambrogio Fassina<sup>2</sup>, Gastone G Nussdorfer<sup>3</sup>,  
Achille C Pessina<sup>4</sup> and Gian Paolo Rossi<sup>4</sup>

<sup>1</sup>Department of Clinical Methodology and Medical, Surgical Technologies, University of Bari, Piazza G Cesare 11, 70124 Bari, Italy

<sup>2</sup>Department of Oncological Sciences: Section of Pathology, University of Padova, Via Giustiniani 2, 35128 Padova, Italy

<sup>3</sup>Department of Human Anatomy and Physiology (Section of Anatomy), University of Padova, Via Gabelli, 35126 Padova, Italy

<sup>4</sup>Department of Clinical and Experimental Medicine, Clinica Medica 4, University of Padova, Via Giustiniani 2, 35128 Padova, Italy

(Requests for offprints should be addressed to G P Rossi; Email: gianpaolo.rossi@unipd.it)

## Abstract

Aldosterone-producing adrenocortical carcinoma (APAC) is a rare cause of hypertension often diagnosed late because of paucity of information. Thus, we delineated its clinical course and survival rates based on two cases referred to us that featured diverging clinical courses, and on a scrutiny of the literature since 1955 when the first case of APAC was identified. Data on demography, imaging results, hormonal assessment, histology, and clinical course were extracted independently by the investigators. We included in our database 58 cases, most presenting with Conn's syndrome. Plasma aldosterone levels were on average increased 14-fold; plasma renin activity was suppressed in 55% of cases. The tumor showed extremely variable size and weight, and no gender or side preference. Metastases were present in 10% of all cases at initial diagnosis and in an additional 48% of cases at follow-up. Median survival was 546 days (95% confidence interval (CI): 240–851); median time to either recurrence or death was 212 days (95% CI: 29–395). No clinical or histological signs predicted survival with Cox regression analysis. We concluded that, although an ominous course with a poor survival rate is common, no sign accurately predicts the course of APAC. Thus, molecular studies to identify diagnostic markers of survival are mandatory.

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## Introduction

Hyperaldosteronism (Conn's syndrome), which is usually sustained by an aldosterone producing adenoma, is the most common cause of curable hypertension (Conn *et al.* 1964, Lim *et al.* 1986, Gordon *et al.* 1994, Rossi *et al.* 1998). In less than 1% of patients with Conn's syndrome an aldosterone producing adrenocortical carcinoma (APAC) can be identified (Vallotton 1996, Ganguly 1998). Over the years, numerous criteria have been proposed to clinically recognize APAC (Brode *et al.* 1962, Weiss *et al.* 1989, Young *et al.* 1990, Icard *et al.* 1992, Schulick & Brennan 1999, Sasano *et al.* 2001), but experience has shown that these criteria may be misleading (Rossi *et al.* 2000).

Adrenocortical tumors are highly prevalent in the general population (Kloos *et al.* 1995, Mantero *et al.*

2000); nonetheless, the differentiation between benign and malignant neoplasms is often difficult (Rossi *et al.* 2000), not only on clinical but even on morphological grounds. Although several criteria have been claimed to allow discrimination between benign and malignant tumors (Lack 1997), including some molecular markers such as the DNA index (Suzuki *et al.* 1992*b*, Gicquel & Le Bouc 1997), the expression of the proliferating cell antigen (Ghnassia *et al.* 1993), the p53 protein (Reincke *et al.* 1994), the adrenal 4 binding protein (Sasano *et al.* 1995), the c-Myc protein (Suzuki *et al.* 1992*a*), or the insulin-like growth factor-II gene (Gicquel & Le Bouc 1997), and the telomerase activity (Mannelli *et al.* 2000), to date none of them has gained wide acceptance because of their poor accuracy, thus resulting in late diagnosis until metastases occurred.

We herein report on two cases of APAC with contrasting histological features and divergent clinical course, which suggested a wide heterogeneity of biological behavior and clinical course. Therefore, we created a database with all cases that have been reported since the first description of APAC in 1955 (Foye 1955) that served to delineate the clinical features, natural history, and survival of patients with APAC.

## Case reports

### Case 1

A 33-year-old woman was referred for evaluation of a right adrenal mass and a 1-month history of mild hypertension. Systolic and diastolic blood pressure ranged between 150 and 160 mmHg and 90 and 95 mmHg respectively. A computed tomography (CT) scan showed a solid, heterogeneous adrenal mass with a maximum diameter of 30 mm. On admission, physical examination was negative; routine laboratory tests, including serum potassium, 24-h urinary catecholamines and low-dose dexamethasone-suppressed plasma cortisol concentrations were all normal. The plasma aldosterone level was elevated both in the sitting (123 pg/ml; normal range: 12–110 pg/ml) and in the upright (415 pg/ml, normal range: 70–220 pg/ml) position but plasma renin activity was not suppressed. At laparotomy removal of a yellowish, 40 × 50 × 55 mm mass was performed; the tumor presented as an ill-defined, large mass with areas of hemorrhage and necrosis. Histopathological examination showed that the tumor was composed of a population of cells with pale, eosinophilic cytoplasm, which were organized in strands and nests, surrounded by collagen (Fig. 1A). Atypical hyperchromatic and pleomorphic nuclei with coarse chromatin and two or three prominent nucleoli were common (Fig. 1B). Many apoptotic bodies and atypical mitotic figures were present in several high power fields. Invasion of the tumor pseudo-capsule and frequent aspects of microscopic vascular invasion were seen. Expression of p53 and Ki67 was evident at immunohistochemistry. Thus, the histological diagnosis was APAC. Nine years after adrenalectomy, the patient is alive, normotensive, normokalemic and with no signs of recurrence of the primary adrenal tumor.

### Case 2

A 63-year-old woman was initially referred to our institution in June 1998 because of marked weakness and hypokalemia. She reported a history of

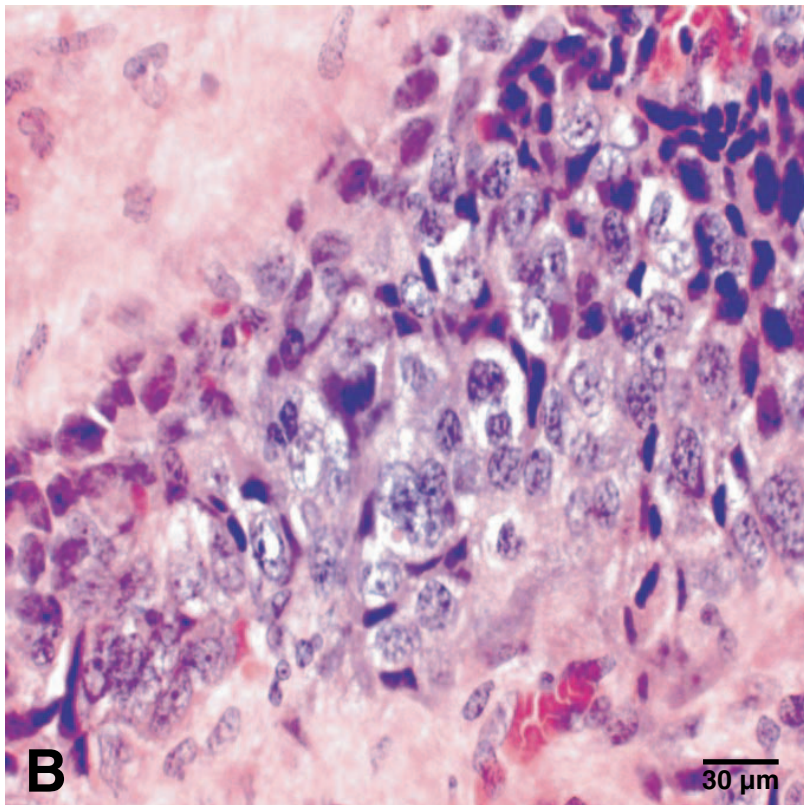
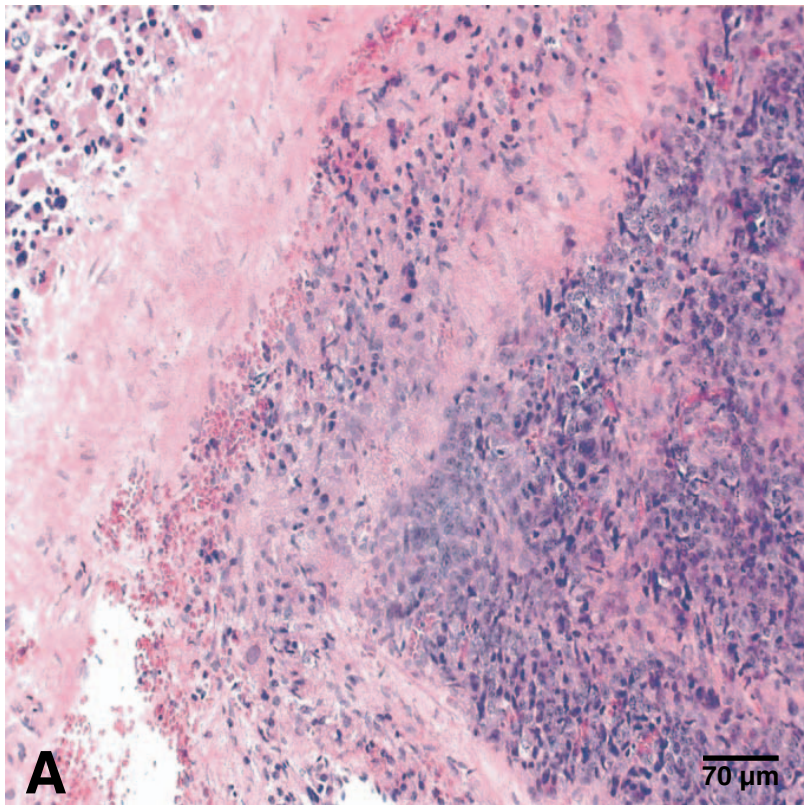
hypertension, with increased plasma aldosterone levels and a low-normal plasma renin activity. CT scan showed a solid and homogeneous 32 × 18 mm adrenal mass and, therefore, a right adrenalectomy was performed. No histological signs of malignancy were noticed and the histological diagnosis was adrenocortical adenoma (Fig. 2A). In February 2000 she was referred again because of marked hypokalemia and uncontrolled hypertension. Physical examination revealed a thoracic ovoid mass of about 75 mm longitudinal diameter, placed on her 10th left rib. A CT scan showed a normal left adrenal gland, but multiple nodular lesions in the liver, a 60 mm osteolytic area in the 10th left rib, and multiple vertebral osteolytic areas. The rib lesion was fine-needle aspirated and examined. Cells were atypical and resembled epithelial cells (Fig. 2B). Since their arrangement suggested an adrenocortical origin, the expression of the aldosterone synthase gene was investigated with RT-PCR that showed gene transcripts (Fig. 2C), thus indicating a diagnosis of metastasis from an APAC. Total body scintigraphy after dexamethasone suppression documented uptake of <sup>75</sup>Se Met cholesterol by the bone lesions. A re-evaluation of the original surgical specimen from the primary tumor showed no signs of malignancy. The patient died 26 months after removal of the primary adrenal gland tumor, from liver failure and a severe gastric hemorrhage (Rossi et al. 2000).

## Methods

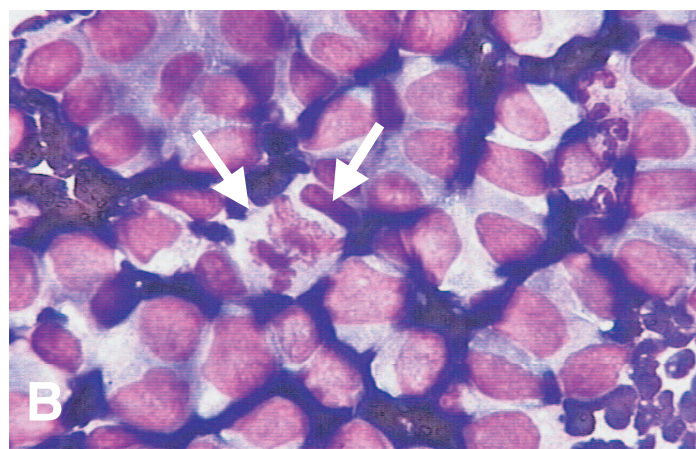
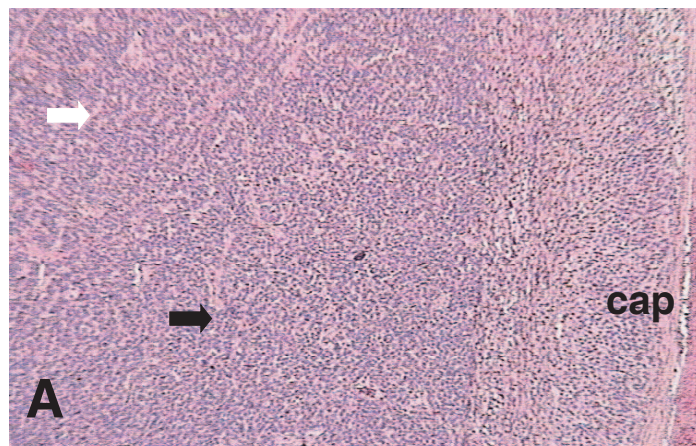
We identified all cases of APAC reported in the literature since 1955, when Foye and Feichtmeier described the first APAC case (Foye 1955), through a Pub Med search and, for older articles published before Pub Med was established, through a meticulous scrutiny of the literature in the Index Medicus. Inclusion criteria were (i) availability of the original paper and (ii) unequivocal diagnosis of APAC. We extracted all relevant available information entailing demography, imaging features, size and weight of the mass, histopathological findings, hormonal data and clinical course. A database was then constructed and used for the analysis.

## Statistical analysis

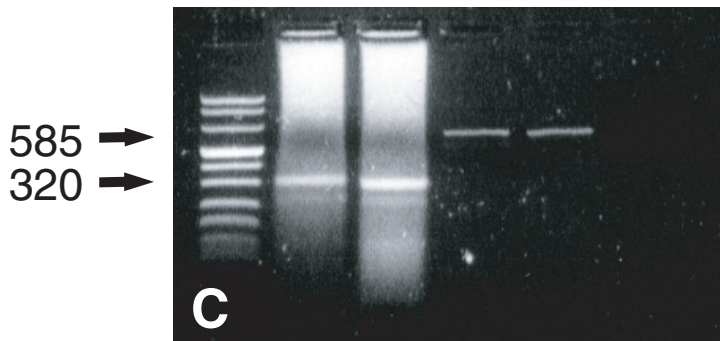
The average ( $\pm$ s.d.) and median (and range) values were calculated as appropriate. Distribution of categorical variables was compared by  $\chi^2$  test; significance was set at  $P < 0.05$ . Survival time was considered as the time elapsing from the initial diagnosis of the adrenal



**Figure 1** Histopathology of the aldosterone producing adrenocortical carcinoma (APAC) from case 1. (A) The large areas of necrosis and hemorrhage present in the tumor are circumscribed by ill-defined, coarse collagen bands (hematoxylin & eosin staining; Scale bar: 70μm). (B) The nuclei are atypical, hyperchromatic and pleomorphic with coarse chromatin and two or three prominent nucleoli; the cytoplasm is ill defined, eosinophilic and pale (hematoxylin & eosin staining; Scale bar: 30μm).



1 2 3 4 5 6



**Figure 2** Histopathology of the primary tumor at first identified as adrenocortical adenoma and of the fine-needle aspirated rib lesion that, together with the finding of aldosterone synthase gene expression, suggested malignancy of the primary tumor in case 2. (A) Section of the adrenocortical neoplasia showing two distinct solid patterns of growth: one with anastomosing columns and cords of cells (white arrow) and the other islet-like (black arrow). No cell and nuclear pleomorphism, no trabecular pattern, no capsular or vascular invasion, no mitoses and necrosis were evident. The intact capsula (cap) surrounded a normal adrenocortical tissue (hematoxylin & eosin staining; Scale bar: 80µm). (B) Cytological sample obtained with fine-needle aspirate from an ovoid mass of the left chest wall. Monomorphic cells with abundant cytoplasm are evident. A mitotic figure is present at the center of the field (arrows) (May-Grunwald-Giemsa staining; Scale bar: 20µm). (C) Ethidium bromide-stained agarose gels showing cDNA amplified with aldosterone synthase gene-specific primers (lanes 2 and 3) from the sample obtained with fine needle aspirate shown in (B). Amplification of cDNA with primers for the housekeeping gene glyceraldehyde-3-phosphate dehydrogenase (GAPDH) (lanes 4 and 5) and no amplification from no DNA template (lane 6) are also shown. The expected size of the amplification products were 585 bp and 320 bp for aldosterone synthase and GAPDH respectively.

mass to censoring at death, or study end. When the date of the initial diagnosis was unavailable, the date of surgery or of first diagnosis of hyperaldosteronism was used instead. Kaplan Meier analysis was used to calculate survival curves and recurrence-free survival. Cox regression analysis was used to evaluate the effects of clinical and histopathological variables on survival.

## Results

### APAC database

The two cases of APAC herein reported had contrasting histological features and divergent clinical courses: the first, despite showing histopathological features of malignancy, showed a benign clinical course with full recovery that persists after 10 years of follow-up. The

second, despite a smaller size and no histopathological features of malignancy, which suggested an initial diagnosis of Conn's adenoma, exhibited an ominous clinical course that led to the patient's death in 26 months. Sixty further cases of APAC could be identified in the literature (Foye 1955, Conn *et al.* 1964, Crane *et al.* 1965, Santander *et al.* 1965, Alterman *et al.* 1969, Brooks *et al.* 1972, Filipecki *et al.* 1972, Six *et al.* 1972, Miyazaki *et al.* 1973, Salassa *et al.* 1975, Revach *et al.* 1977, Boers *et al.* 1981, Grim *et al.* 1981, Taylor *et al.* 1982, Slee *et al.* 1983, Telner 1983, Arteaga *et al.* 1984, Greathouse *et al.* 1984, Levine *et al.* 1984, Luscher *et al.* 1984, Sakashita *et al.* 1984, Stone *et al.* 1984, Scott *et al.* 1986, Valentini *et al.* 1986, Farge *et al.* 1987, Fraser *et al.* 1987, Isles *et al.* 1987, Tenschert *et al.* 1987, Weiss *et al.* 1989, Touitou *et al.* 1992, Barksdale *et al.* 1993, Boscaro *et al.* 1995, Weingartner *et al.* 1995, Sakai *et al.* 1997, Taylor *et al.* 1997, Muthusethupathi *et al.* 1998, Siren *et al.* 1998, Yamazaki *et al.* 1998, Deckers *et al.* 1999, Shen *et al.* 1999, Parajo *et al.* 2000, Rossi *et al.* 2000, Yoshimoto *et al.* 2000, Dixon & Bing 2001), four were excluded because either papers were not accessible (Kandrac & Zikanova 1957, Shah *et al.* 1975), or the diagnosis of APAC was considered questionable (Salassa *et al.* 1975). Therefore, 58 cases, including the two described herein, were entered in the database.

### Demographic and clinical features

The large majority of information on demography and biological features, summarized in Table 1, was available in 80% of the cases. The peak of incidence of APAC was between 40 and 49 years of age (median: 44

years, range: 17–79 years) and a trend towards a preference for women (57%) over men (43%) and for the right over the left side (58% vs 42%) was found.

The hallmarks of Conn's syndrome, e.g. hypertension and hypokalemia, were found in all except three cases, that had hypokalemia but not hypertension (Muthusethupathi *et al.* 1998, Yamazaki *et al.* 1998), and in the present case 1 that had hypertension but not hypokalemia.

### Tumor size and hormonal features

Tumor size and weight ranged widely, from 25 to 150 mm and from 6.3 to 1250 g (median values 70 mm and 248 g respectively). However, pathological staging according to TNM classification was unfeasible because of lack of the necessary information in most reports.

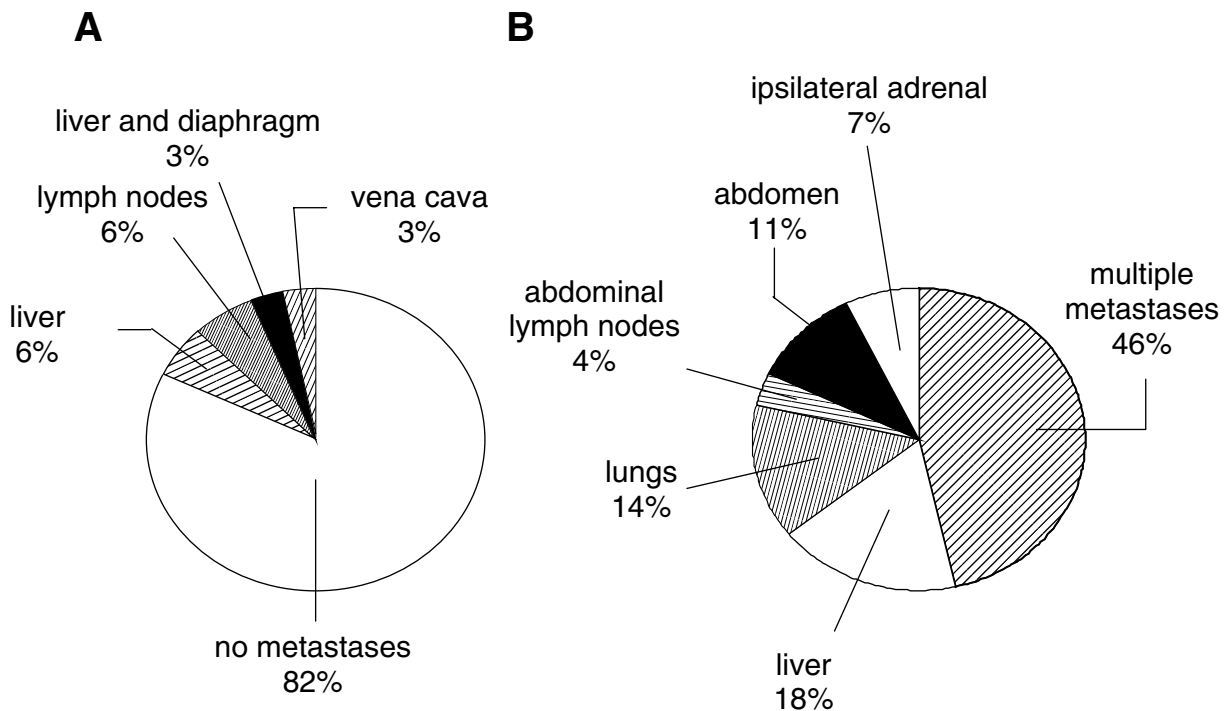
Hyperaldosteronism was found in all cases, but plasma aldosterone levels were reported in 35 cases. Since the range of plasma normal values of aldosterone markedly differed between studies, we calculated the percentage increase from the upper normal value in 34 cases for which both values and normal range were available, and found an average increase of 14-fold. Plasma renin activity was suppressed in 55% of all cases; however, values were not reported in 27% of cases.

Most authors measured glucocorticoids and other steroids in plasma. They reported slightly elevated levels of plasma cortisol in 10% of cases, whereas the plasma levels of dehydro-epiandrosterone sulfate were generally normal. The excretion rate of 17-hydroxycorticoids and 17-ketosteroids was found to be abnormally high in 8% and 6% of cases respectively; however, it was measured in only 28 cases. Other steroid metabolites or

**Table 1** Demographic and clinical features. Median and range are given for age, diameter and weight; average and range are given for % increase of plasma aldosterone levels; means  $\pm$  s.e. are given for systolic and diastolic blood pressure, and plasma potassium levels

Variables	Value
Age (years)	44 (17–79)
Gender (M/F/NA) (n)	21/27/10
Side of tumour (R/L/NA) (n)	26/18/14
Maximum tumor diameter (mm)	70 (25–150)
Tumor mass weight (g)	248 (6.3–1250)
Systolic blood pressure (mmHg)	188 $\pm$ 4
Diastolic blood pressure (mmHg)	111 $\pm$ 2
Hypertension (n of cases; %)	55 (95%)
Plasma potassium levels (mmEq/l)	2.30 $\pm$ 0.08
Hypokalemia (present/absent/NA) (n, %)	56 (96%)/1 (1.7%)/1 (1.7%)
Low plasma renin activity (present/absent/NA) (n, %)	32 (55%)/10 (17%)/16 (27%)
% increase of aldosterone from the upper normal value	+ 14 (1.1–333)
Adrenalectomy (performed/not performed/NA)	52/4/2

M, male; F, female; NA, not available; R, right; L, left.



**Figure 3** Localization of metastases in APAC. (A) Pie graph shows occurrence of metastases at the time of the initial diagnosis. No metastases were observed in 82% of cases. In the remaining cases metastases were localized in liver (6%), lymph nodes (6%), vena cava (3%), or in liver and diaphragm (3%). (B) Localization of metastases at the time of the recurrence of the disease. In most cases (46%) they developed in multiple sites. Single localization occurred in liver, lungs, abdomen, ipsilateral adrenal and abdominal lymph nodes. Values were calculated as percentage of cases developing metastases.

precursors were measured in too few cases to warrant any conclusion.

### Imaging characteristics

Intravenous pyelography, angiography, and/or ultrasonography were used to visualize the mass in 20 cases before CT became available. These tests showed either a highly vascularized tissue or a heterogeneous mass due to the presence of necrotic areas and/or calcifications in 45% of cases. CT was performed in 38% of cases, while no information on magnetic resonance (MR) features of APAC is available. One or more CT signs evocative of malignancy, such as heterogeneous density, calcifications, capsular invasion, organ displacement and/or intra-mass hemorrhages, were found in less than half (46%) of cases.

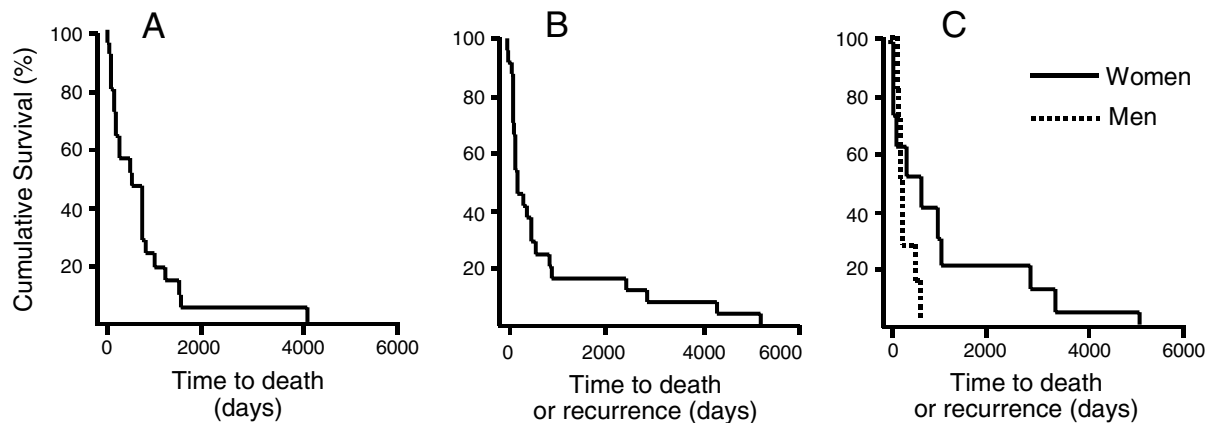
### Pathology

Adrenalectomy was performed in 90% of all cases; two cases were medically treated (Crane *et al.* 1965, Telner 1983), in two the tumor was detected only at necropsy

(Santander *et al.* 1965, Alterman *et al.* 1969), and in another two there was no information on treatment. The macroscopic examination of the surgical specimens revealed calcifications, areas of necrosis and/or hemorrhages and/or invasion of adjacent tissues in 70% of 28 cases for which information was available. There was no information on occurrence of metastases in 43% of the 58 cases at the time of the initial diagnosis; in 6 of the 34 that had detailed information on metastases they localized to liver (6%), lymph nodes (6%), vena cava (3%), or to liver and diaphragm (3%) (Fig. 3A). Microscopically, at least one of the typical signs of malignancy, such as trabecular pattern, nuclear grade, mitotic rate, atypical mitoses, necrosis, invasion of capsule and/or of venous or sinusoidal structures (Lack 1997), were noticed in 79% of all cases. Interestingly, in two cases, including our case 2, there were no signs of malignancy (Dixon & Bing 2001).

### Effects of surgery and clinical course

Information on follow-up after surgery or initial diagnosis was available in only 48 cases, but the length of



**Figure 4** Survival and recurrence-free survival rates in APAC. Kaplan Meier analysis showed that median survival, considered as time elapsing from diagnosis to death or study end, was 546 days (A). The median recurrence-free survival, that was calculated as time elapsing from diagnosis to either recurrence or death, was 212 days (B). Recurrence-free survival according to gender showed a worse trend in men than in women (C), but this did not attain statistical significance. In all three analyses, when the date of initial diagnosis was not specified, the date of surgery or, if this date was also missing, of diagnosis of hyperaldosteronism, were considered instead.

available follow-up ranged widely and was sometimes very short (median value 15 months; range 1–132 months). Adrenalectomy was reported to initially cure both hypokalemia and hypertension in most cases; a mild form of hypertension persisted in 15% of cases and hypokalemia only in one case. Interestingly, one patient was normotensive after adrenalectomy despite persistent hyperaldosteronism (Muthusethupathi *et al.* 1998).

Recurrence of the disease was described in 48% of all cases, while no signs of recurrence were documented in 34% of patients; in the remaining information was unavailable. The organs involved with metastases (Fig. 3B) included liver (18%), lung(s) (14%), abdominal lymph nodes (4%), abdomen (11%), and ipsilateral adrenal site (7%). In 46% of cases that developed metastases at follow-up multiple sites were involved, very often the liver (10/12), lung(s) (6/12) and kidney (4/12). In one case the site of recurrence was not specified (Conn *et al.* 1964). The histology of metastatic tissue was provided in only 8 studies. In all but two cases, including our case 2, cytological features resembled those of the primary tumor, with only a greater degree of nuclear pleiomorphism (Dixon & Bing 2001). In most patients, metastases were associated with recurrence of hypertension and hypokalemia; however, in one patient liver metastases with no increase in aldosterone or hypokalemia were documented (Dixon & Bing 2001).

### Kaplan Meier and Cox analyses

At Kaplan Meier analysis the median survival was 546 days (95% confidence interval (CI): 240–851) (Fig. 4A); a shorter time (212 days) was found when considering time to either recurrence or death (95% CI: 29–395; Fig. 4B). Cox regression showed that age, hypokalemia, weight, diameter of the adrenal mass, histological signs of malignancy or metastases at the time of diagnosis did not predict survival. A trend towards a worse recurrence-free survival was seen in men compared with women (Fig. 4C), but it did not attain statistical significance.

### Discussion

Adrenocortical carcinomas causing arterial hypertension with an exclusive oversecretion of mineralocorticoids are exceedingly rare, although they might be underreported with ensuing underestimation of their prevalence. Aldosterone overproduction often concurs with that of other steroids, including glucocorticoids, estrogens or androgens, thus leading to Cushing's syndrome, virilization or feminization (Icard *et al.* 1992, Barzon *et al.* 1997, Schulick & Brennan 1999). Moreover, most cases of Conn's syndrome are accounted for by a unilateral adenoma or uni- or bilateral adrenal hyperplasia (Young 1999). Accordingly, the rarity of APAC might explain the lack of

information on biological behavior, clinical features, natural history, and survival of APAC patients.

Over the past decade in a relatively large series of consecutive cases of Conn's syndrome we observed two cases of APAC, which had contrasting histological features and divergent clinical courses, and differed to some extent also from those previously reported. The first had histological features consistent with a malignant neoplasm, but was long-term cured by adrenalectomy. The second initially showed no histological evidence of malignancy at adrenalectomy and was diagnosed as a Conn's adenoma (Rossi *et al.* 2000), but 18 months later manifested itself again with Conn's syndrome and a widespread metastatic disorder that was fatal in a few months. In both cases, at CT scan the tumor size was smaller than 40 mm in diameter and therefore did not have the large size that has been proposed as an indication for adrenalectomy. Thus, it would appear that neither the size at CT scan nor the histological features accurately predict clinical course and outcome in APAC.

We therefore built a database that served to outline the features of this disease based on a search of all published APAC cases. This allowed us to determine that the peak incidence of APAC was in the fourth decade, e.g. similar to that reported for adrenocortical carcinoma (Schulick & Brennan 1999, Wajchenberg *et al.* 2000), Conn's adenoma, and bilateral hyperplasia (Melby 1972, Lack 1997). A trend towards a predominance of APAC in women, similar to that reported for adrenocortical carcinoma (Schulick & Brennan 1999) and aldosterone producing adenoma (APA) (Grant *et al.* 1984, Lack 1997) was noticed.

In most cases the clinical picture featured the classical signs of Conn's syndrome, e.g. hypertension and hypokalemia. The latter, when marked, was reported to be associated with weakness and diffuse muscular pain, but these signs and symptoms, being common in hyperaldosteronism due to adrenocortical adenoma or hyperplasia, are not helpful in identifying APAC. Moreover, other symptoms, such as fever or weight loss, that are frequent in adrenocortical carcinoma (Pommier & Brennan 1992, Schulick & Brennan 1999), were rarely found in APAC.

A large tumor size is usually taken as a presumptive sign of malignancy in clinical practice (Greathouse *et al.* 1984, Young 1997). In contrast, our present meta-analysis documented that very small tumors can also be malignant, since 9% of all cases, including our case 2, were smaller than 3 cm (Greathouse *et al.* 1984, Weingartner *et al.* 1995, Deckers *et al.* 1999, Dixon & Bing 2001), and developed metastases (Deckers *et al.* 1999, Rossi *et al.* 2000, Dixon & Bing 2001). As

regards side, we found a trend towards a predominance of APAC in the right versus the left side that can be at variance with the left side prevalence of adrenocortical carcinomas (Schulick & Brennan 1999).

Thus, it would appear that the demographic features of the patients, the size and the side of the tumor do not allow unequivocal identification of APAC nor do they predict recurrence after surgery.

The concomitant production of steroids causing a variety of clinical syndromes has been contended to be another criterion that should alert physicians to the presence of APAC. However, production of glucocorticoids or sex steroids was reported only in a few patients and, therefore, it should be acknowledged that there is no solid evidence supporting the usefulness of this criterion.

Of interest, normal values of plasma aldosterone and/or potassium were described in some patients with metastases of histologically confirmed APAC (Brooks *et al.* 1972, Dixon & Bing 2001), suggesting that APAC might change their biology over time into poorly differentiated tumors that, while originating metastases, no longer overproduce aldosterone.

## CT and pathological findings

Only 46% of the 28 cases with CT results showed at least one CT sign of malignancy, but these features were deemed to be non specific and are often seen in other metastatic neoplasms or granulomatous infections (Schulick & Brennan 1999). Whether the MR features could be more specific remains unsettled, because of the lack of information on this technology in APAC.

As regards histology, at least two well-documented cases (Rossi *et al.* 2000, Dixon & Bing 2001) showed that signs of malignancy may be lacking. In our case 2, the primary neoplasm showed no signs of malignancy and the diagnosis of APAC was retrospectively made when metastases were documented. In striking contrast, our case 1 showed clear signs of malignancy, but exhibited a benign clinical course, thus indicating that histology might be misleading in predicting survival. Recently, attention has been focused on the potential usefulness of molecular and cellular markers, such as PCNA, Ki67 and DNA aneuploidy, for diagnosing adrenocortical carcinoma (Sasano *et al.* 2001). At present, however, the evidence supporting their usefulness for diagnosing APAC is scant.

## Metastases

Disappointingly enough, the demonstration of metastases at initial diagnosis or follow-up would seem to



be the only clear-cut criterion for diagnosing APAC. In this meta-analysis metastases were seen in 10% of all cases at initial diagnosis and in 48% at follow-up. These rates do not differ considerably from those seen in adrenocortical carcinomas (Icard *et al.* 1992).

### Clinical course

We used statistical techniques to determine survival curves and to calculate median time to recurrence and death for APAC since there was no information on this important issue. Kaplan Meier analysis showed a median survival of 546 days that is similar to the value of 435 found in a cohort of 105 patient with adrenocortical carcinoma (Luton *et al.* 1990). We also sought to identify the predictors of survival with Cox analysis and found that neither clinical signs nor histological features of malignancy were accurate predictors of survival.

### Perspectives and conclusion

This study shows that the clinical features of APAC are quite variable, although an ominous clinical course with a poor survival was common. Hence, a high degree of alert for the presence of APAC should be exercised even when all common criteria suggestive of malignancy are lacking. We successfully used a molecular analysis to diagnose metastasis in case 2 and we are currently exploiting the use of DNA microarray technology for gene expression profiling in order to identify gene markers that can unequivocally discriminate carcinomas from adenomas. Given the rarity of APAC an international Register and a tissue bank of documented cases could be a major step for better clarifying the features of this unusual cause of hypertension and for understanding the complexity of its molecular mechanisms.

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