Isolated Production of Aldosterone by a Malignant Adrenal Carcinoma

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A 45-year-old female developed hypertension and hypokalemia. Elevated plasma aldosterone and suppressed plasma renin levels were measured with no evidence for glucocorticoid or androgen abnormalities. A left adrenal tumor was removed that showed histologic criteria for malignancy. It is commonly taught that malignant adrenal tumors are recognized by their multiple hormone production. However, isolated aldosterone production by a carcinoma can occur and requires close follow-up observation and therapy for this highly malignant tumor.

In 1955, Conn et al. described the syndrome of primary hyperaldosteronism [1] and one year later reported a patient with an aldosterone-producing adrenal cortical adenoma producing primary hyperaldosteronism, which has come to be known as "Conn syndrome" [2]. Adrenal adenomas account for approximately 70 percent, bilateral adrenal hyperplasia for 25 to 30 percent, and adrenal carcinoma for less than 5 percent of all cases of Conn's syndrome [3]. The first such carcinoma was reported in 1955 by Foye and Feichtmeir [4], just after Conn's original report. Adrenal cortical carcinoma is of itself very rare and in a review of one hundred and thirty-eight such cases by Hutter et al. in 1966 [5], none had overproduction of aldosterone or evidence for hypermineralocorticoidism.

Secreting adrenal carcinomas predominantly produce glucocorticoids or their precursors rather than mineralocorticoids. In those adrenal carcinomas that do produce aldosterone, other steroid hormones are also produced in excess [3,6,7,27]. These multihormone-producing carcinomas do not fit the rigid criteria which Conn [2] proposed specifically to exclude tumors associated with clinical or chemical evidence of androgen or glucocorticoid overproduction. Therefore, even the first case by Foye and Feichtmeir [4] does not fulfill Conn's criteria because of chemical evidence of excess glucocorticoid secretion.

Mineralocorticoid excess as the only biochemical evidence of excessive hormone secretion by an adrenocortical carcinoma is distinctly uncommon [3]. Thus, a patient who presents with hyperaldosteronism and who has no evidence for other steroid abnormalities most likely has a benign adrenal tumor.

This paper reports a patient and reviews the previously published literature of isolated aldosterone hypersecretion due to a malignant adrenal carcinoma.

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CASE REPORT

A 45-year-old white female noted paresthesias, carpal-pedal spasm, and muscle weakness for several months. The new onset of hypertension was noted with a blood pressure of 220/120 in both arms, without orthostatic change. Her blood pressure had been normal one year earlier at her last examination. Her only medication was occasional acetaminophen. She was 63 inches tall and weighed 115 pounds. She had normal body hair, fat distribution, and pigmentation. There were no striae, buffalo hump, moon facies, or peripheral edema. She had a normal female habitus and internal pelvic exam. There were no signs of virilization. Fundoscopic examination was normal. Neurologic examination, including visual fields, was within normal limits.

She had had three full-term pregnancies and three spontaneous abortions. There was no history of hypertension during any of her pregnancies. She developed transient hypothyroidism after her last pregnancy and had been on replacement therapy until three years ago. Since that time she has required no therapy. She had had a transabdominal hysterectomy with a right salpingo-oophorectomy for dysfunctional uterine bleeding at age thirty-four. An incidental appendectomy was also done at that time.

Her brother and father have chronic hypertension and her mother had a history of "thyroid disease" and died at age 53 of a ruptured aortic aneurysm. There was no family history of adrenal disease, kidney stone, diabetes, or pituitary dysfunction.

Laboratory Data

Initial laboratory evaluation revealed a fasting glucose of 92 mg %, hematocrit of 41 percent, white blood count of 5,000 with a normal differential, serum sodium 151 mEq/L, potassium 1.7 mEq/L, chloride 104 mEq/L, bicarbonate 32 mEq/L, calcium 9.2 mg/dl, phosphate 3.4 mg/dl, and creatinine of 1.0 mg/dl. Other laboratory values included a normal "spot urine" for 5-HIAA and normal thyroid function studies. EKG revealed tall U waves, but otherwise was normal. Hormone levels are listed in Table 1.

Clinical Course

A presumptive diagnosis of primary aldosteronism was made and she was placed on amiloride, 5 mg twice a day, but her serum potassium concentration remained low. On spironolactone, 100 mg three times daily, plus 80 mEq of KCL, three times daily, her blood pressure and serum electrolytes normalized. A computerized axial tomogram revealed a 3.2 cm left adrenal mass (Fig. 1). The right adrenal was normal. The patient was admitted to the Hospital of St. Raphael for surgery.

One day pre-operatively the spironolactone and potassium were stopped in anticipation of post-operative hyperkalemia [11]. At surgery, a left adrenalectomy was performed via a left flank incision. The adrenal gland weighed 20 grams and did not have the yellowish color typical of a benign adrenal adenoma (Fig. 2). Histologic examination revealed vascular (Fig. 3) and capsular invasion (Fig. 4) and many atypical mitotic figures (Fig. 5); a diagnosis of an adrenal cortical carcinoma was made. The non-involved adrenal was normal in appearance and was not atrophic. Post-operatively, potassium supplementation was needed for five days as she remained somewhat hypokalemic (2.9 mEq/L). Her 24-hour urine potassium excretion was 22 mEq K+/24 hours and her blood pressure corrected without therapy. A liver-spleen scan and chest X-ray were normal with no evidence of metastatic disease.
### ALDOSTERONE SECRETION BY CARCINOMAS

| Laboratory Data for Our Patient | Normal Values |
|---------------------------------|---------------|
| Before Therapy | One Day | Two Days | Seven Days | Five Weeks | Six Months | Post-Op | Post-Op |
| Plasma renin activity | 0.1 | 0.2 | 1.4 | 3.3 | 1.5 | 1.4 | 9.0 | 5.6 |
| Plasma aldosterone | 104 | 4.5 | 7.0 | 9.0 | 10.0 | 1.0 | 8.0 | 5.0 |
| 25-hour urine: | | | | | | | | |
| Creatinine | 0.9 | 4.95 | 11.3 | 33 | 3.5 | 3.5 | 8.0 | 5.0 |
| Potassium | 11.3 | 11.3 | 11.3 | 11.3 | 11.3 | 11.3 | 11.3 | 11.3 |
| 17 Hydroxysteroids | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 | 3.5 |
| Metanephrites | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 | 0.6 |
| Plasma cortisol 8 AM (by RIA) | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Serum: | | | | | | | | |
| Sodium | 151 | 151 | 151 | 151 | 151 | 151 | 151 | 151 |
| Potassium | 4.1 | 4.1 | 4.1 | 4.1 | 4.1 | 4.1 | 4.1 | 4.1 |
| Chloride | 110 | 110 | 110 | 110 | 110 | 110 | 110 | 110 |
| Bicarbonate | 26 | 26 | 26 | 26 | 26 | 26 | 26 | 26 |
FIG. 1. Computerized axial tomography showing a 3.2 cm left adrenal tumor (arrow).

FIG. 2. Twenty-gram left adrenal gland.

FIG. 3. Malignant cells within adrenal vein (arrow).
ALDOSTERONE SECRETION BY CARCINOMAS

DISCUSSION

Benign adrenal adenomas usually have a homogeneous golden-yellow color and weigh less than six grams [12]. Adrenal cortical carcinomas have soft, friable nodular areas, frequently have areas of necrosis and hemorrhage, and can weigh as much as 2,000 grams [12].

Microscopically it usually is difficult to distinguish benign from malignant tumors, but a number of criteria have been used to distinguish adenoma from carcinoma [3,13,14,15]. These include: (1) capsular invasion, (2) vascular invasion, which may cause vessel occlusion and thrombosis, (3) presence of mitoses, (4) presence of bizarre giant cells (large cells with abundant acidophilic cytoplasm and bizarre hyperchromatic nuclei and multinucleated forms), and (5) presence of spindling of tumor cells.

These features may be absent in malignant adrenal tumors or may be present in some benign tumors. Hence, the only reliable and universally accepted criterion of malignancy is the presence of metastases [12].
Adrenal cortical cancers of all types are highly malignant. They frequently recur, even after presumed total excision, with metastases found in the liver (60 percent), regional lymph nodes (40 percent), and lungs (40 percent) [14]. One-half of the 38 patients in the series of Lipsett et al. [7] were dead after two years, and in the study by Huvos et al. [14] 30 of 34 patients were dead within three years.

Occasionally, adrenal cortical carcinomas produce hypoglycemia, polycythemia, or the syndrome of inappropriate antidiuretic hormone [7] (none of which was present in our patient). The degree of hypokalemia and the urinary aldosterone excretion rate tend to be greater in patients with malignant tumors [3] but an individual patient cannot clearly be categorized as having a benign lesion or a malignancy on these criteria alone. Likewise, a good response to spironolactone does not preclude a malignant lesion as the cause of the hypermineralocorticism.

It is widely accepted clinical teaching that an adrenal carcinoma does not produce only aldosterone and that hyperaldosteronism due to a carcinoma can be suspected pre-operatively by chemical or clinical evidence of androgen and/or glucocorticoid excess [27]. Although the majority of aldosterone-producing adrenal carcinomas fit such a description, there are only seven cases of adrenal carcinoma, in addition to our patient, which solely produced aldosterone [3,8,9,10,26].

In a series of 105 patients presenting with primary aldosteronism, Salassa et al. [3] reported six patients with large adrenocortical tumors. Four of these tumors had histological features of malignancy while two had "benign" histology. These last two patients had isolated aldosterone overproduction as their only abnormality and have survived for more than nine years. The four malignant tumors ranged in size from 250 to 1,050 grams and three of the four had serum potassium levels less than 2.5 mEq/L. Each had an elevated 24-hour urinary aldosterone and normal 24-hour urinary 17-ketosteroids. One of the four, however, had an elevated 24-hour urinary 17-ketogenic steroid level and elevated tetrahydro-11-deoxycortisol. Thus only three patients of this series had a malignant adrenal tumor producing only aldosterone.

Our patient, one of Salassa's cases for whom data is given (his case number 5), and four other cases of isolated hyperaldosteronism due to malignant adrenal tumor are summarized in Table 2. Five were females, one was male. All had similar laboratory abnormalities: profound hypokalemia, hypernatremia, elevated plasma or urinary aldosterone, suppressed renin activity, and normal 17-hydroxy and 17-ketosteroids. However, very little hormone data is available in the report of Santander et al. [10]. The urinary $K^+$ loss was profound in our patient yet within normal limits in Revach et al.'s case [9] although her urinary $K^+$ was inappropriately high in relation to her serum $K^+$ of 2.4 [16]. Of interest is the normal blood pressure in Shah et al.'s patient [8]. Greathouse et al. report the most hormonal data for their case [26].

Santander et al. [10] were unable to measure urinary aldosterone or plasma renin activity, as these were unavailable to them in their country (Venezuela). This case assumes a diagnosis of an adrenal cortical carcinoma secreting only mineralocorticoids. Whether it secreted aldosterone or a different mineralocorticoid [17] or even had hypertension and hypokalemia on a non-adrenal basis is unproven.

There have been a number of cases of malignant adrenal carcinoma which clinically presented as isolated hypermineralocorticoidism [4,10,18,19,20,21,22,23], i.e., arterial hypertension and hypokalemic metabolic alkalosis without clinical but with laboratory evidence of hypercortisolism or hyperandrogenism. Most of these cases have been reviewed by Alterman et al. [18], who presented an additional case with a mixed hormonal output. In this same article they reviewed ten other cases. Nine had
### TABLE 2
Cases of Isolated Hyperaldosteronism Due to Malignant Adrenal Tumor

|                        | Our Patient | Shah et al. [8] 1975 | Revach et al. [9] 1977 | Santender et al. [10] 1965 | Salassa et al. [3] 1975 | Greathouse et al. [26] 1984 |
|------------------------|-------------|-----------------------|------------------------|---------------------------|------------------------|---------------------------|
| Age/Sex                | 45/F        | 68/F                  | 31/F                   | 50/F                      | 52/M                   | 47/F                      |
| Serum K+               | NA+         | 151                   | 145                    | 145                       | 148                    | NA                        |
|                        | K+          | 1.7                   | 1.2                    | 2.4                       | 2.6                    | 2.5                       |
| Urine K+ mEq/35 hour   | NA          | 495                   | NA                     | 46                        | NA                     | NA                        |
| before RX              |             |                       |                        |                           |                        | 48                        |
| Blood pressure         |             | 220/120               | 130/78                 | 220/130                   | 160/110                | "Elevated" 200/100        |
| Plasma aldosterone     |             | 104                   | NA                     | 111                       | NA                     | NA                        |
| (NL 9–28 upright)      |             |                       |                        |                           |                        | 25(n14–16)                |
| ng/ml                  |             |                       |                        |                           |                        |                           |
| P.R.A. (ng/ml/hr)      |             |                       |                        |                           |                        |                           |
| (NL – 1.13–3.95 upright)|            |                       |                        |                           |                        |                           |
| .01                    | NA          | .01                   | NA                     | 0                         | NA                     | 2.6 ng/ml 0.38            |
| 24-hour urine:         |             |                       |                        |                           |                        |                           |
| Aldosterone (NL – 4–13 μg/24°) | NA | 95                    | 108                    | NA                        | 211                    | 43(n12–26)                |
| 17-KS (mg/24°)         |             |                       |                        |                           |                        |                           |
| (NL – 5–15)            | 11.3        | "Normal"              | 2.7                    | 11.5                      | 8.4                    | 6.8                       |
| 17-OH (mg/24°)         |             |                       |                        |                           |                        |                           |
| (NL – 7–20)            | 3.5         | "Normal"              | 20                     | 9.3                       | 5.4 (ketogenic)        | 11.5                      |
| Plasma cortisol by RIA |             |                       |                        |                           |                        |                           |
| (NL – 10–25 μg/dl)     |             |                       |                        |                           |                        |                           |
| Surgery                | 22          | "Normal"              | 12                     | NA                        | 14.1                   | 14–21                     |
| 3.2 cm left adrenal CA |             | 3 cm right adrenal CA | 6 cm right adrenal CA  | 90-gm right adrenal CA   | 900-gm right adrenal CA| 3 × 3 cm right adrenal CA |
| None                   | Alive at 24 months | Died within one year | Died 2½ years after surgery from liver metastases | Died within 3 months of surgery | Liver, lungs | None | Alive after 24 months |
| Metastases at surgery  |             |                       |                        |                           |                        |                           |
| Outcome                |             |                       |                        |                           |                        |                           |

(NL) = Normal range  CA = Carcinoma  NA = Not available
a mixed secretory pattern and only one had normal 24-hour urinary 17-hydroxy and 17-ketosteroids (the case of Santander et al. [10]). Other cases of adrenal cortical carcinoma secreting multiple hormones have been reported [24,25].

The demonstration of excessive production of multiple hormones by an adrenal tumor is important since it suggests the presence of a malignant carcinoma. However, our case plus six others reported in the literature [3,8,9,10,26] demonstrate that isolated aldosterone can rarely be produced by an adrenal cortical carcinoma. Failure to recognize this association may lead to an erroneous diagnosis of a benign adrenal adenoma and delay operative intervention and proper follow-up. If one waits for the presence of metastases to establish the diagnosis of malignant adrenal cortical carcinoma, the chance of curative surgery may be lost.

Our patient’s tumor fulfilled most of the histologic criteria for carcinoma [12,13,14,15] and consequently she will require lifelong supervision for recurrence of disease. Our patient as well as the other reported cases [3,8,9,10,26] indicate that isolated hyperaldosteronism may be caused by a malignant adrenal cortical carcinoma.

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REFERENCES

1. Conn JW: Primary aldosteronism. J Lab Clin Med 45:661–664, 1955
2. Conn JW: Primary aldosteronism—a new entity. Ann Int Med 44:1–15, 1956
3. Salassa RM, et al: Primary aldosteronism and malignant adrenocortical neoplasia. Trans Amer Clin and Clin Assoc 86:163–169, 1975
4. Foye LV Jr, Feichtmeir TV: Adrenal cortical carcinoma producing solely mineralocorticoid effect. Amer J Med 19:966–975, 1955
5. Hutter AM, Kayhoe EE: Adrenocortical carcinoma—clinical findings in 138 patients. Amer J Med 41:572–580, 1966
6. Hajjar RH, et al: Adrenal cortical carcinoma—a study of 32 cases. Cancer 35:549–554, 1975
7. Lipsett MB, Hertz R, Ross GT: Clinical and pathophyslogic aspects of adrenocortical carcinoma. Amer J Med 35:374–383, 1963
8. Shah S, et al: Aldosteronism—hypokalemia adenocarcinoma of the adrenal gland. Journal of the Kansas Medical Society 76:277–278, 1975
9. Revach Moshe, et al: Hyperaldosteronism caused by adrenal cortical carcinoma. Israel J Med Sci 13:1123–1128, 1977
10. Santander S, Gonzalez A, Suarez JA: Case of probable mineralocorticoid excess without hypercortisolism due to a carcinoma of the adrenal cortex. J Clin Endocr 25:1429–1435, 1965
11. Biglieri EG, Slaton PE, Silen WS, Galen M, Forsham PH: Postoperative studies of adrenal function in primary aldosteronism. J Clin Endocr 26:553–558, 1966
12. Neville AM, Symington T: Pathology of primary aldosteronism. Cancer 19:1854–1868, 1966
13. Tang CL, Gray GI: Adrenocortical neoplasms—prognosis and morphology. Urology 5:691–695, 1975
14. Huvos AG, Hadju SI, et al: Adrenal cortical carcinoma—clinopathologic study of 34 cases. Cancer 25:354–361, 1970
15. Kay S: Hyperplasia and neoplasia of the adrenal gland. Pathol Annu 11:103–139, 1976
16. Schwartz WB, Relman A: The nephropathology of potassium depletion—a clinical and pathological entity. New Eng J Med 225:195–203, 1956
17. Mader JJ, Lloyd TJ: Spontaneous hypopotassemia, hypomagnesemia, alkalosis and tetany due to hypersecretion of corticosterone-like mineralocorticoids. Amer J Med 19:976–988, 1955
18. Alterman SL, et al: Primary adrenocortical carcinoma causing aldosteronism. Cancer 24:602–609, 1969
19. Zimmerman B, Moran WH, Rosenberg JC, Kennedy BJ, Frey RJ: Physiologic and surgical problems in the management of primary aldosteronism. Ann Surg 150:653–664, 1959
20. Brooks RV, McSwiney RR, Prunty FT, Wood FJ: Potassium deficiency of renal and adrenal origin. Amer J Med 23:391–407, 1957
21. Crane MG, Harris JJ, Herber R: Primary aldosteronism due to an adrenal carcinoma. Ann Intern Med 63:494–503, 1965
22. Feldman S, Ravera JJ: Arterial hypertension caused by a primary malignant adrenocortical tumor. Thorax 10:284–289, 1961
23. Knapton PJ: Hypokalemic alkalosis in adrenal carcinoma. Lancet ii:346, 1965
24. Six R, Leclercq R, Noeninckx F: Hypermineralocorticoidism the sole clinical manifestation of an adrenal cortical carcinoma. Acta Clin Belg 27:426–434, 1975
25. Grimm CE, et al: Hyperaldosteronism due to unsuspected adrenal carcinoma—discovery during investigation of hypertension in a young woman. J Urology 126:783–786, 1981
26. Greathouse EJ, McDermott MT, Kidd GS, Hofeldt FD: Pure primary hyperaldosteronism due to adrenal cortical carcinoma. Amer J Med 76:1132–1136, 1984
27. Hogan TF, Gilchrist KW, Westring DW, Cotrin DL: A clinical and pathological study of adrenal carcinoma. Cancer 45:2880–2883, 1980