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Original Paper

Incidentally Found Adrenocortical Carcinoma. A Study of 21 Patients

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The frequency of adrenocortical carcinoma was studied in a group of 311 incidentally discovered adrenal tumours. Clinical characteristics were also analysed. Ultrasound scan and computed tomography were the main imaging techniques used. Hormonal examinations were also carried out. The patients with an adrenal tumour diameter greater than or equal to 4.0 cm, and those with excess steroid production were recommended for surgery. Of 131 patients treated with surgery, adrenocortical carcinoma was diagnosed in 21 cases. The diameter of these tumours ranged between 3.2 and 20.0 cm. The majority of these were hormonally inactive, but, in some cases increased corticosteroid secretion was noted. In 17/21 patients, mitotane was administered following surgery, with a good response in 13 cases. These 21 cases were compared with a group of 51 patients with clinically overt adrenocortical carcinoma. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: adrenocortical carcinoma, tumour size, ultrasound scan, computed tomography, incidentally found adrenal tumour, corticosteroids, mitotane
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INTRODUCTION

In the last 11 years, 311 patients with incidentally discovered adrenal tumours were referred to the Department of Endocrinology (Centre for Postgraduate Medical Education) in Warsaw. A group of 208 such patients was recently described [1]. The majority of tumours were detected by ultrasound and thereafter confirmed by computed tomography (CT). Only in 11 cases was CT the first imaging procedure. The main diagnostic aim was to select the patients for surgical treatment, i.e. those with malignant and/or hormonally active tumours [2].

In this report, we describe our observations on 21 patients with microscopically proven adrenocortical carcinoma and compare them with other cases of incidental adrenal tumours, as well as with a group of adrenocortical cancer of 'non-incidental' type. Surgery followed by mitotane administration was the main method of therapy in the patients with adrenocortical carcinoma. Mitotane (o,p′-DDD, i.e. 1,1-dichlorodiphenyldichloroethane) inhibits intramitochondrial conversion of cholesterol to pregnenolone and conversion of 11-desoxycortisol to cortisol [3, 4]. It is also a compound capable of producing selective adrenocortical necrosis, both in the adrenal tumour and in metastases. This drug may only work following metabolic activation, o,p′-DDA (o,p′-dichlorodiphenyl acetic acid) being the end product of the presumed metabolic activating pathway [5].

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PATIENTS AND METHODS

Among 311 patients with incidentally found adrenal masses, there were 227 women and 84 men, aged 14–76 years (Table 1). The second group comprised 51 patients with clinically detected adrenocortical carcinoma, referred to our department within the last 31 years [6].

Imaging procedures included ultrasound scan, CT scan, and less frequently magnetic resonance imaging (MRI). Carcinomas diagnosed in the 1960s were examined by radiological studies, including arteriography (if necessary).

The endocrine examinations performed in all cases comprised radioimmunoassay (RIA) measurements of serum cortisol levels and urinary excretion of 17-hydroxycorticosteroids (17-OHCS) and 17-ketosteroids (17-KS), determined by the Silber and Porter and Zimmerman methods, respectively. In most patients, additional hormonal examinations

Table 1. *Data of* 311 *patients with incidentally found adrenal tumour and* 51 *patients with clinically detected adrenocortical carcinoma*

Diagnosis	Number of patients		Female/male ratio	Age (years)		Tumour size (cm)	
	Female	Male		Range	Mean	Range	Mean
Incidental							
Benign tumour ($n = 265$)	208	57	3.6	23–76	50.2	0.8–21.0	3.2
Carcinoma ($n = 21$)	13	8	1.6	14–70	43.1	3.2–20.0	13.0
Metastatic tumour ($n = 25$)	6	19	0.3	45–73	60.1	3.0–15.0	5.2
Non-incidental							
Carcinoma ($n = 51$)	43	8	5.4	13–71	41.2	5.0–17.0	11.0

(RIA) were carried out, such as serum concentrations of dehydroepiandrosterone sulphate (DHEA-S), androstendione, testosterone and, in selected patients, 17-hydroxyprogesterone (17-OHP), oestradiol (E_2), aldosterone, renin activity, growth hormone (GH), growth hormone releasing hormone (GHRH), as well as the corticotrophin releasing hormone (CRH)-test and dexamethasone suppression test, as described previously [1].

Surgery was performed on 131 patients and in 21 of these, pathological examination revealed adrenocortical carcinoma, accordingly to the criteria of Hough and colleagues [7]. When analysing the decision to carry out an ultrasound scan, the following causes were revealed: malaise (5 patients), abdominal or lumbar pain (4 patients), muscular weakness (2 patients), and in single cases: gallstone colic, haematuria of uncertain origin, erythrocytosis, thyrotoxicosis, paroxysmal atrial fibrillation, amenorrhoea intermittent in a patient with the polycystic ovaries syndrome. In 4 cases, the examination was performed for control purposes. Staging was based on clinical data and radiological examinations at the time of diagnosis. Localised, regional or metastatic disease was diagnosed according to the Surveillance, Epidemiology and End Results Classification [8]. Metastases appearing within 3 months after the removal of the primary tumour were considered to be present at the time of surgery.

Adjuvant therapy included mitotane ($n = 17$); cisplatin and etoposide ($n = 1$); or radioactive cobalt ($n = 1$). For regional and distant disease, the initial daily dose of 3.0 g of mitotane was quickly increased to 8.0–10.0 g for approximately 2 weeks and then was decreased gradually. The daily dose used for long-term treatment was 3.0–5.0 g. For patients with localised disease, the daily dose did not exceed 4.0 g. In cases misdiagnosed at the time of surgery, the dose of mitotane was increased to 8.0–10.0 g by day with the appearance of metastases or regional recurrence. 14 patients received mitotane directly after surgery and 2 patients within the next 2–3 months. 1 patient, referred to our department 2 years after the removal of the carcinoma, with a recurrent tumour progressing even after interferon gamma administration and six cycles of chemotherapy, was also given mitotane. The mitotane serum concentration in the cases with regional and distant disease was maintained between 15 and 25 μg/ml (the measurements were kindly carried out at the laboratory of the Centre of Child Health by M. Filipek). Routine replacement therapy with hydrocortisone and fludrocortisone was instituted during mitotane therapy.

Table 2. *Main clinical features in* 72 *patients with adrenocortical carcinoma*

Features	Incidental	Non-incidental
Cushing's syndrome	0	26
Prae–Cushing's syndrome	1	0
Virilisation/hypertension	0	2
Virilisation	0	2
Hypertension	0	1
Gynaecomastia	0	1
Myasthenia	0	1
Pathological fractures	0	2
Acromegalic signs	1	0
Palpable tumour	0	1
Lumbar pain	2	4
Abdominal pain	2	2
Weight loss, weakness	3	2
Retroperitoneal haemorrhage	0	2

RESULTS

Demographic details and tumour size in patients are shown in Table 1. In the incidental group, the carcinoma was localised in the right side in 11 patients and in the left side in 10 other cases. In the non-incidental group, the carcinoma was localised in the right side in 25 patients, in the left side in 25 patients and bilaterally in 1 patient. Most incidental malignant adrenal tumours in our series had a diameter of 8 cm or more, but 6 patients had tumours of 3.2, 4.0, 5.4, 6.0, 7.0 and 7.6 cm. Some benign tumours had a diameter of 10.0 cm or more. The main symptoms and signs in the two groups are summarised in Table 2. Table 3 provides a comparison of

Table 3. *Staging in* 72 *cases of adrenocortical carcinoma*

Stage	Incidental number (%)	Non-incidental number (%)
Localised disease	8 (38)	13 (25)
Regional disease	4 (19)	11 (22)
Distant disease	9 (43)	27 (53)

Table 4. *Increased steroid values in the patients with adrenocortical carcinoma*

Steroids	Number of patients	
	Incidental	Non-incidental
17-OHCS	3	33
17-KS	3	30
Cortisol	1	33
DHEA-S	1	7/20*
Testosterone	1	9/24*

*Examinations carried out in the last 5–7 years. 17-OHCS, 17-hydroxycorticosteroids; 17-KS, 17-ketosteroids; DHEA-S, dehydroepiandrosterone sulphate.

Table 5. Results of treatment of 21 patients with incidentally found adrenocortical carcinoma

Treatment	Survival (months)	Survivors			Dead	
		n	Free of disease	Mean survival time (months)	*n*	Mean survival time (months)
Surgery ($n=2$)	2; 60	1	1*	60	1	2
Surgery + adjuvant therapy ($n=19$)	5–74	13	9	44	7	16
+ mitotane ($n=17$)	12–74	13	9	44	4	18
+ cisplatin + etoposide ($n=1$)	20	0			1	20
+ ^{60}Co-therapy ($n=1$)	5	0			1	5

*Urinary 17-hydroxycorticosteroid excretion rose above the upper normal limit in the last 2 months of follow-up. 5 months later (65 months after resection of an adrenocortical carcinoma in the right side), a small adrenal tumour in the left side was found in CT; microscopically: adrenocortical carcinoma. Mitotane has been administered.

staging. In both groups, there were cases misdiagnosed at the time of surgery: in 9 patients classified as having localised disease, metastases appeared over the next few months and in 2 other patients, regional recurrence took place.

Table 4 demonstrates increased steroid values in both groups. In a 32-year-old woman with significantly raised 17-KS excretion, without concomitant virilisation, chromatographic analysis revealed increased urine content of fetal-type androgens, 16-OH-androstendione and androstendiol. Six months after incomplete surgery, testosterone and androstendione levels rose and virilisation appeared. Similarly, her serum GH level, from 49 μg/l (normal 1.0–5.0 μg/l) before tumour resection, rose to 190 μg/l in the metastatic phase, her plasma GHRH level being 110 pg/ml (normal 10–70 pg/ml) [6].

In Table 5, the results of treatment in the group of 21 patients with incidental adrenocortical carcinoma are summarised. 9 of 13 survivors treated with mitotane were free of disease at the time of the study. 6 had received mitotane immediately after the operation, which in a female patient included right hepatic lobe removal and in a male patient, nephrectomy; in the other 3 patients, this drug was administered 2–4 months after surgery. In a 60-year-old man, free of disease for 13 months on mitotane, a recurrence of the adrenal tumour was found within 2 months of the patient not taking the drug. Re-introduction of mitotane therapy resulted in a decrease in tumour size. In the patient with regional disease, in whom mitotane therapy was started 2 years after surgery, the diameter of the recurrent tumour diminished from 12.0 to 6.0 cm on CT. In the patient treated only by surgery, who seemed to be free of disease over the next 5 years, the urinary 17-OHCS excretion rose, exceeding the upper normal limit in the last 2 months. 6 patients died because of metastatic dissemination. In a 25-year-old woman, a fulminant metastatic dissemination took place immediately following radiotherapy. A 73-year-old woman died because of cardiac arrhythmia in the third year of mitotane administration.

DISCUSSION

Adrenocortical carcinoma has long been believed to be a rare tumour [9–14], but the introduction of new imaging procedures may modify this opinion. The majority of our patients, since 1966, have been admitted to our department because of fulminant progression of Cushing's syndrome or virilisation. In the last 8 years, clinically occult adrenocortical carcinomas have also been referred to our department. The 21 incidentally found adrenocortical carcinomas constitute 29% of our group of 72 cases with this diagnosis. In our first report on incidental adrenal tumours [15], we did not observe any malignant tumours, but in a subsequent study [1] there were 18 cases among 208 patients. The frequency of incidentally discovered adrenocortical carcinoma reported here, i.e. 21/311 cases (6.8%), is not high, but indicates that this tumour is not rare. Kloos and colleagues [16], in their review of available literature, define the frequency of these tumours as ranging from 0 to 25%. Our observations indicate that clinically occult adrenocortical carcinoma is more frequent in male patients (female/male ratio = 1.6) than is the non-incidental (female/male ratio 5.4) and benign tumour (female/male ratio = 3.6). The mean age of the patients with either non-incidental or incidental adrenocortical carcinoma was lower than patients with benign or metastatic disease. The higher frequency of benign adrenal masses with age has been mentioned in the literature [17], but not analysed in clinical reports and commentaries [18–23]. Tumour size was variable between tumour types and did not necessarily relate to malignancy [1, 24].

The characteristics of malignant adrenal masses on imaging examinations have been described by other authors [16, 25]. Hormonal examinations were less useful in diagnosing incidental adrenal tumours, but elevated excretion of 17-OHCS and 17-KS was noted in 2 patients without clinical features of steroid excess. The 17-OHCS urine content could be high due to an increased desoxycortisol secretion, while the 17-KS fraction could contain fetal-type androgens. As in our previous report [1], we could not confirm the diagnostic value of DHEA-S estimation.

The analysis of the clinical course in both groups of adrenocortical carcinoma revealed that distant disease was frequent at the time of diagnosis, but was lower in the incidental group (9/12, 43%) than in the non-incidental group (27/51, 53%). The incidence of localised disease was higher in patients with incidentally found tumours (8/21, 38%, versus 13/51, 25%). It is worth mentioning that of 10 patients diagnosed at surgery as having localised disease, metastasis was revealed in 8 patients over the next few months and in the 2 other patients, a local recurrence developed. The possibility of incorrect classification was the reason we decided to treat all patients with adrenocortical carcinoma with mitotane as soon as possible after surgery. Our past observations [6] have indicated that the true diagnosis in some cases was delayed, so delaying the administration of mitotane, contributing to a poor prognosis. The microscopic evaluation of the adrenal tumour during surgery would facilitate the decision concerning mitotane administration.

In conclusion, we presume that adrenocortical carcinoma occurs more frequently than is generally believed. A routine ultrasound scan should be performed in all adults to detect adrenal tumours early. The ultrasound finding should be confirmed by CT scan before surgery. Early mitotane administration in the cases of adrenocortical carcinoma improves prognosis.

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