# ADRENAL CORTICAL CARCINOMA AND CUSHING'S SYNDROME: A REPORT OF TWO CASES AND A REVIEW OF THE LITERATURE

ACK Fok, AYS Tan, APY Chong, PPB Yeo

**SYNOPSIS**

**Carcinoma of the adrenal cortex causing Cushing's syndrome has been described but is an uncommon condition in clinical practice locally. Two such patients have been seen in the department, one of whom had virilising features in addition to the stigmate of Cushing's syndrome. The subject of Cushing's syndrome due to carcinoma of the adrenal cortex is reviewed.**

**SING MED J. 1988; 29: 513 – 518**

## INTRODUCTION

In 1932, Cushing described a syndrome of weakness, purplish striae, central obesity, amenorrhoea and hypertension which he ascribed to an adenoma of the pituitary gland.

Since then it has been found that the common denominator of this syndrome is an excess of cortisol which may be the consequence of disease in the pituitary gland, of the adrenal glands or other organs. Commonly it is iatrogenic, the result of ACTH or steriod therapy for other medical disorders.

Cortical tumours of the adrenal glands causing Cushing's syndrome are distinctly rare in clinical practice. Over a eight year period in a busy department such as ours, we have seen only two such patiensts, both of whom were local Chinese women. This clinical features are described and we evaluate our experience with aminoglutethimide in the treatment of the disorder.

**University Department of Medicine**
**Singapore General Hospital**
**Singapore 0316**

ACK Fok, MMed(Int Med), MRCP(UK) Registrar

**Department of Paediatrics**
**National University Hospital**
**Lower Kent Ridge Road**
**Singapore 0511**

AYS Tan, MBBS, Resident

APY Chong, MBBS, Pathologist
Department of Medicine
National University Hospital

PPB Yeo, MD, FRCP, FRACP, Associate Professor

**Address for correspondence: Dr Fok**

## CASE REPORT ONE

TML, a 34 year old Chinese lady presented with complaints of amenorrhoea of 14 months associated with progressive abdominal distension, abdominal striae, development of a red round face with acne and proximal muscle weakness of 10 months.

Clinical examination revealed Cushingoid features (Fig 1) with truncal obesity, buffalo hump and purplish abdominal striae (Fig 2) a moon facies (Fig 3). Hirsute features were absent. The patient was hypertensive (BP 160/115 mmHg) with cardiomegaly and grade 2 hypertensive retinopathy. A rounded ballotable mass was found in the right hypochondrium. Proximal weakness involving the muscles of the pelvic girdle was present.

Investigations showed Hb 20.8 g/dl, Haematocrit 59.9%, ESR 2 mm/hr, TW 10.5 x 109/L, Platelets 145 x 109/L, Urea 26 mg/dl, Sodium 126 mEq/L, Potassium 3.2 mEq/L, Chloride 89 mEq/L, Calcium 9.0 mg/dl, Phosphate 4.4 mg/dl. Oral GTT: 65 – 204 – 187 mg/dl. Plasma cortisol levels at 0800 hrs nd 2400 hours were 29 and 23 ug/dl respectively. There was no suppression of cortisol levels with low dose dexamethasone, the level being 28 and 37 ug/dl prior to and following dexamethasone respectively. ECG revealed left ventricular hypertrophy and the chest X ray showed cardiomegaly. There was no enlargement of the pituitary fossa on skull X-ray. The plain abdominal film showed a right renal shadow that was displaced downwards by a suprarenal mass. Aortography and renal arteriography showed a large tumour of the right adrenal gland which derived its blood supply from the inferior and middle adrenal arteries. Characteristic tumour circulation was noted with patchy ares suggesting necrotic areas within the tumour. The inferior vena cava and liver were not involved by tumour. Plasma cortisol from the right adrenal vein was assayed to be 63 ug/dl and that from the left 30 ug/dl.

Her blood pressure was controlled with Tab methyl-dopa 125 mg tds and her impaired glucose tolerance with 1500 Calorie diet.

A right adrenalectomy via a thoraco-lumbar approach was performed. A tumour weighing 2.17 kg and measuring 18 x 12 x 8 cm was removed (Fig 4). Pathological examination

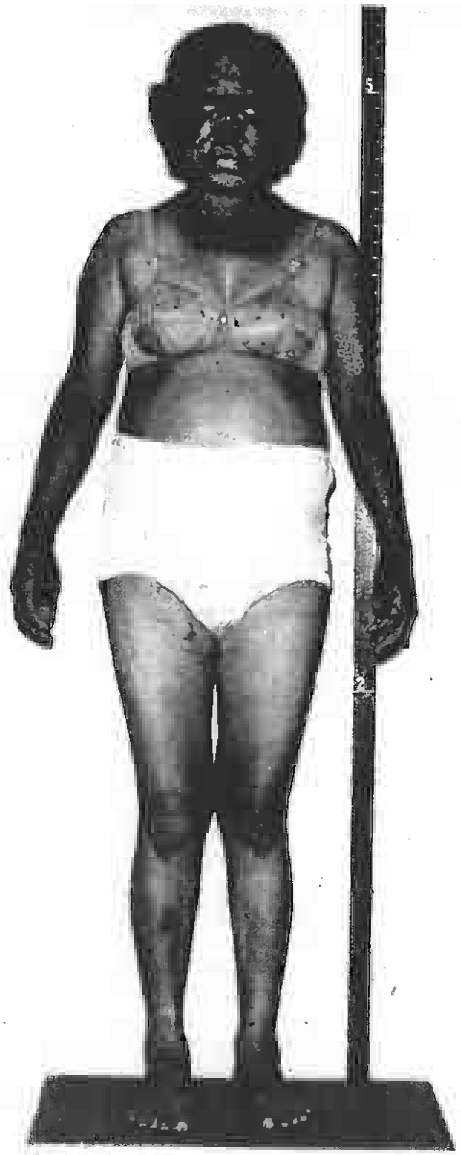


Fig 1 : Patient 1 at time of presentation

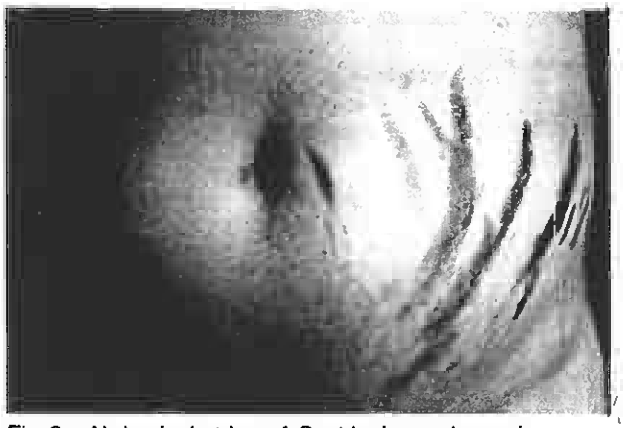


Fig 2 : Abdominal striae of Cushing's syndrome in Patient 1

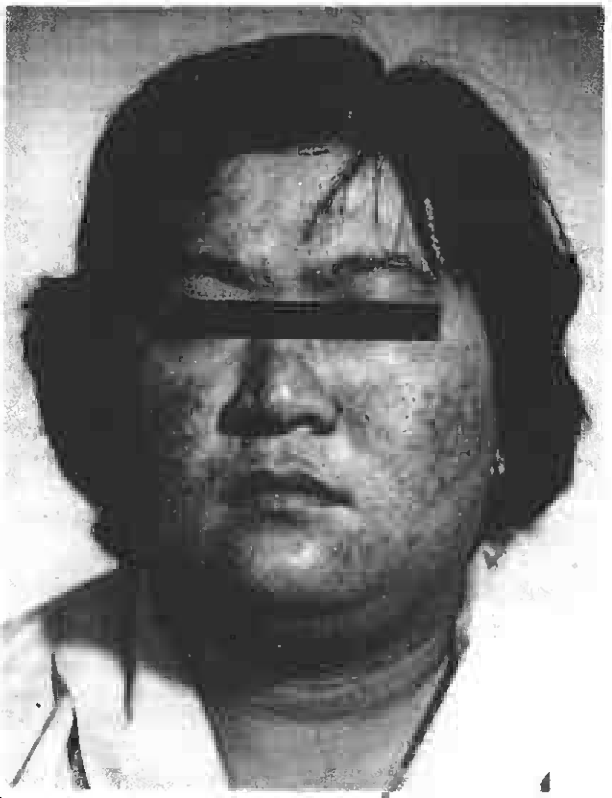


Fig 3 : Picture showing Cushingoid facies. From Patient 1

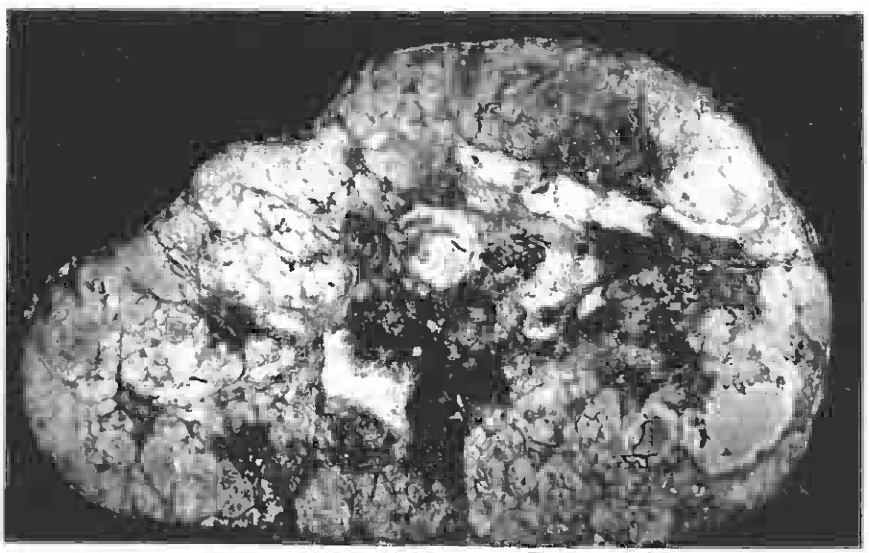
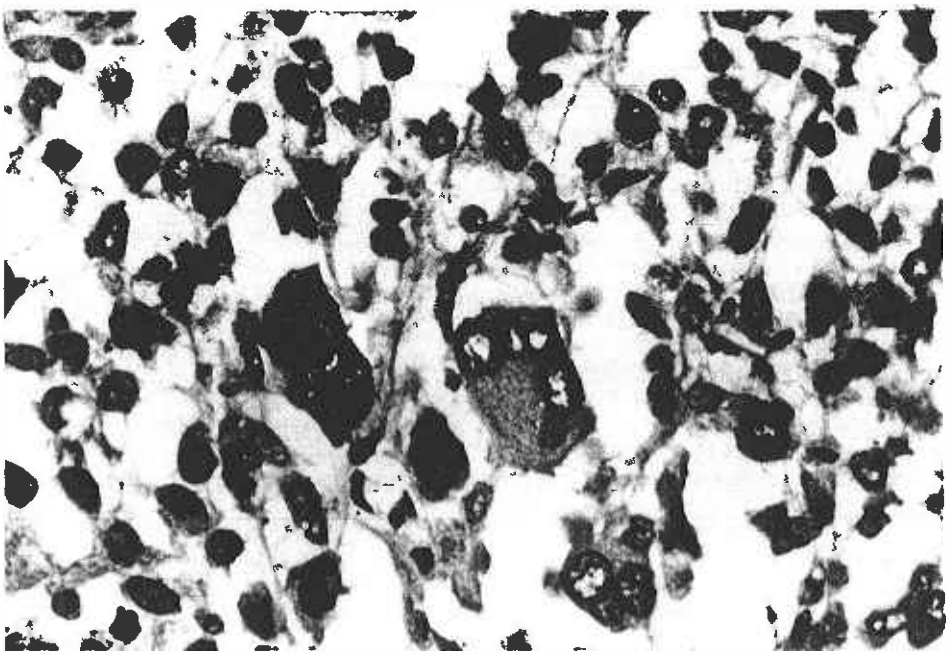


Fig 4 : Gross appearance of right adrenal tumour weighting 2.17 kg remored from Patient 1

Fig 5 : Pleomorphic and tumour giant cells of adrenal cortical carcinoma. Section from Case 2. (Haematoxylin-eosin x 640)



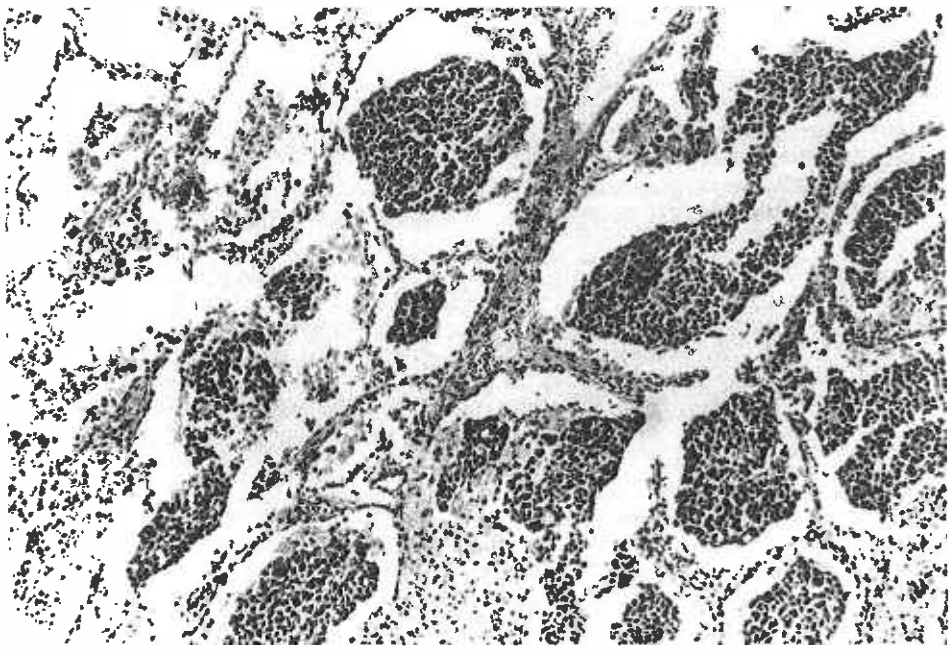


Fig 6 : Section of tumour metastasis in the lung of Patient 2, showing features similar to the primary cortical tumour of the left adrenal (Haematoxylin-eosin x 63)

showed complete replacement of the adrenal gland by a cellular cortical carcinoma with cellular pleomorphism and multinucleate giant cells. Large areas of tumour necrosis with focal flecks of calcification were seen.

Post-operatively, the patient was treated with intravenous hydrocortisone and subsequently maintained on cortisone acetate. Four months after surgery, she was taken off steriods. Her Cushingoid features were noted to have regressed. Fifteen months postoperatively, metastases to the lung were detected. She was started on Cyclophosphamide for a duration of 28 months whereupon she defaulted treatment.

**CASE REPORT TWO**

LAK, a 44 year old housewife, presented with proximal limb weakness, weight loss, effort dyspnoea and right hypochondrial pain of three month's duration. She became amenorrhoeic at the age of 41 years. A past history of nasopharyngeal carcinoma poven by pastnasal biopsy was treated with a course of radiotherapy eight years previously.

Clinical examination showed the patient to have Cushingoid features with hirsuitism. The patient had moon facies, was plethoric and had abdominal striae. Male pattern baldness was noted. Clitoromegaly was absent. The liver was enlarged and a ballotable mass 10 cm below the left costal margin was detected in the left loin. The patient was anicteric. Proximal muscle weakness was marked. There was no recurrence of NPC on ENT clearance.

Investigations revealed Hb 16.0 g/dl, Total White 35.9 x 109/L, Urea 39 mg/dl, Sodium 137 mEq/L, Potassium 3.1 mEq/l, Chloride 91 mEq/L, Creatinine 1.0 mg/dl. She was found to be diabetic. 75 gm Oral GTT was 111 — 230 — 374 mg/dl. Liver function showed Total Protein 5.5 g/dl, Albumin 3.5 g/dl, Bilirubin 0.5 mg/dl, SAP 189 IU/L, GPT 33 IU/L, GOT 51 IU/L. Calcium 8.4 mg/dl, Phosphate 2.8 mg/dl. Blood gas was normal.

The chest X ray showed coin lesions in the lower and middle zones of the left lung field and the middle zone of the right lung field. The liver scan showed a markedly enlarged liver with multiple filling defects consistent with secondaries. Needle biopsy of the coin lesions in the lung revealed malignant cells consistent with an undifferentiated carcinoma.

Plasma cortisol at 2400 hours and 0800 hours were 41.8 and 45.1 ug/dl respectively (normal range 8 — 23 ug/dl). The 24 hour urinary free cortisol was 2450 ug/day (normal range 80 — 380). The 24 hour urinary 17 — ketosteroids was 122.7 mg/day (normal range 5 — 17) and 24 hour urinary 17 hydroxy corticosteroids was 53.7 mg/day (range 6 — 20). Plasma ACTH level was 11 pg/ml (normal range 20-80).

Multiple lucent areas in the liver consistent with secondaries was evident on the CT Scan of the abdomen with a large adrenal mass on the left displacing the left kidney downwards. Angiography confirmed the presence of a large tumour of adrenal origin. For technical reasons, adrenal venous sampling was not carried out.

A diagosis of virilising adreno-cortical carcinoma with metastases to the liver and lung was made. The patient was offered surgery but refused consent.

She was started on Tab aminogluthetimide 750 mg/day. On the fourthe day of treatment, she developed severe hypotension and hypoglycaemia. The blood pressure fell suddenly to 60 mm Hg systolic and the blood sugar plunged to less than 10 mg/dl. This resulted in a fall off her bed resulting in a large scalp haematoma from trauma to the head. A CT scan of the brain done showed no intracerebral haemorrhage resulting from the fall. No brain metastases were evident on the CT scan films.

The aminoglutethimide was stopped temporarily and restarted upon her recovery at a lower dosage of 250 mg/day. Despite the lower dosage, the patient again went into hypoglycaemia and hypotension, which necessitated the use of inotropic agents to maintain blood pressure.

Treatment with aminoglutethimide was terminated and the patient managed conservatively. She died three months after presentation of liver failure consequent upon metastatic disease.

A post-mortem examination revealed a normal right adrenal gland weighing 6.5 grammes. The left adrenal gland was replaced by a large tumour weighing 800 g measuring 14 x 15 x 7 cm. It was adherent to the spleen, left renal fascia and to the tail of the pancreas. Section of the tumour showed a variegated appearance with solid yellowish areas admixed with haemorrhagic and necrotic areas. No normal adrenal tissue was identifiable.

The liver was enlarged and studded with multiple secondaries in both lobes which on section showed the same macroscopic features as in the adrenal. The lungs were similarly affected as were the paratracheal, para-aortic and splenic lymph nodes. Secondary tumour was demonstrated in the bone marrow.

Histological examination showed the left adrenal to be completely replaced by an undifferentiated tumour with large pleomorphic cells, high mitotic index, giant cells and arranged in sheets and trabeculae (Fig 5). There was a great deal of haemorrhage and necrosis. Similar microscopic features were seen in the sections of lung (Fig 6), liver, bone marrow and lymph nodes.

Electron microscopy demonstrated the presence of mitochondriae with tubular cisternae in the cytoplasm of tumour cells.

**DISCUSSION**

Adreno-cortical carcinoma is for the clinician a difficult condition to treat. The difficulty stems in part from the rarity of the disease, which makes it unfeasible for trials and studies on any large scale from which conclusions can be drawn, Hutter and Kayhoe (1) in a review of statistics from three large cancer registries, calculate the incidence of adreno-cortical carcinoma to be two per million population per year.

Despite its rarity, there are a few large series published on this condition(1)(2)(6). It is known that adrenal cortical carcinoma occurs in all age groups up to the eighth decade. In one series of 49 patients by King et al (2) the age at diagnosis varied from 5 months to 77 years at the time of presentation with a mean of 34 years. The average age of presentation was 28.7 years for females while that for males was almost a decade later at 38.2 years.

In two series (1)(3) it was reported that the condition is for more prevalent in females.

Adreno-cortical tumours occurred with equal frequency in each adrenal gland. The commonest sites of metastases were the lung and the liver whereas metastases to the brain were rare. Metastases retain the same functional status as the primary tumour.

The commonest non-endocrinological presenting symptoms were that of abdominal pain and weakness, while the most common sign was that of an abdominal mass.

The peculiar feature of such tumours is its association with endocrinological syndromes. A functioning adrenal cortical carcinoma most commonly produces 17 ketosteriods (17 KS) resulting in features of virilisation as was seen in our second patient. There is a strong association between the production of 17 KS and the finding of carcinoma on histology. The association of 17 KS production with a benign adenoma is by comparison rare.

The earlier age of presentation in females highlighted earlier on is thought to be attributable to the fact that the effects of 17 KS production are not apparent in males but plainly manifest in females. Hence in the former, the tumour is not detected till late in its course when its comes to light from a non-endocrinological presentation.

The second most common group of steriods produced by functioning adreno-cortical carcinomas is 17-hydroxycorticosteriods which manifest as Cushing's syndrome and which again is more easily observed in females. One would expect therefore that in patients with functioning tumour, one would find more females than males.

This hypothesis is supported by Lipsett's review(3) of nine series in which he showd that 52 of 81 patients with adrenal cortical carcinoma without manifestation of hormone excess were male compared to 88 of 103 patients with Cushing's syndrome who were females.

Less commonly, other classes of hormones are produced. Feminisation due to oestrogen production was reported by Hutter and Kayhoe(1) to occur in 12% of patients who presented wit hendocrinological symptoms. Recognition of this syndrome only in men is to be expected, as feminisation is impossible to detect in females.

Aldosterone producing tumours are also reported manifesting as hypertension with hypokalaemic alkalosis,

Surgery is the primary treatment for this condition. Even when the disease is extensive with metastases, there is a case for surgery to debulk the tumour. This procedure makes subsequent chemotherapy and its associated side effects more manageable because of lower doses of cytotoxics that will be required.

Most reviews on surgical management of this tumour highlight the need for optimal preoperative management in terms of diabetic control and blood pressure control if the best results are to be obtained in operative mortality and morbidity.

In a review of their experience with 10 patients with adrenal cortical carcinoma and Cushing's syndrome who underwent surgery, Scott et al (4) report that the finding of limited extent of the tumour at the time of operation permitted a curative resection in 6 patients. Remission of the features of Cushing's syndrome occurred in each of these 6 patients for periods ranging from 10 months to 12 years. Three patients developed recurrence of the tumour and Cushing's syndrome. Three other patients remained alive and free of Cushing's syndrome at 10 months, 3 years and 9 years after initial resection of the tumour.

Two patients had extensive metastases and following palliative resection, succumbed to the disease within 8 to 10 months of the operation. The remaining patient did not survive the operation. These figures although small, illustrate the bad prognosis with extensive disease and the need for early detection and treatment if the patient is to be given a chance for cure.

Radiotherapy as a modality of treatment is a poor choice as the tumour is relatively radio-resistant.

Chemotherapy remains the better alternative in palliative management. Apart from the usual cytotoxics used in the treatment of malignant disease, the discovery of 1,1 dichloro-2-(o-chlorophenyl)-2-(p-chlorophenyl)-ethane, also known as o,p' DDD or mitotane as a potent alternative has caused several studies to be carried out on this drug.

Hutter and Kayhoe(5) showed that mitotane caused a reduction in abnormal steroid excretion as well as demonstrable reduction in tumour mass in a significant number of patients. However Hajjar et al (6) reported no statistical difference in survival rates between those treated surgically and those treated by surgery combined with chemotherapy. Hence the overall efficacy of this drug remains controversial.

Chemotherapeutic agents other than mitotane were tried in individual cases with no beneficial effect (Hajjar et al)(6). These included methotrexate, 5-fluorouracil, cyclophosphamide, vinblastine, MCCNU and adriamycin. Our first patient was treated with cyclophosphamide but unfortunately was lost to follow up.

Aminogluthimide was first used as an anticonvulsant drug in the USA in 1960, but an adverse number of side effects led to its withdrawal by the FDA. It was subsequently shown to inhibit adrenal steroid biosynthesis and used to treat disorders requiring "medical adrenalectomy"(7). It has no anti-tumour activity. Its effect is to block a number of hydroxylations required for steriod synthesis by binding competitively to cytchrome P-450 (8). The drug particularly inhibits the conversion of cholesterol to delta 5-pregnenolone by inhibiting cholesterol side chain cleavage, in so doing, effecting a chemical adrenalectomy.

It was hoped that in the second patient, such a course of treatment would achieve the twin aims of adequate preoperative management and of rendering the patient symptomatically better. On the first occasion that aminoglutethimide was started, precipitous drops in blood pressure and blood sugar levels occured suddenly and without warning. This was totally unexpected as such an adverse reaction has to our knowledge not been reported previously. The starting dosage of 750 mg/day was an average starting dose, comparable to the doses used by other investigators(9)(10).

In our anecdotal experience, aminoglutethimide was a poor choice in this patient. Other centres however report varying degrees of success with this drug, Misbin et al (9) in a study of 21 patients with metastatic adrena-cortical carcinoma treated with aminoglutethimide reported a clinical and biochemical response in 62% of patients, a biochemical response in 14% of patients (giving a total response rate of 76%) compared with no response in 24% of patients.

Prognosis is uniformly poor. This is an extremely malignant disease with a five year survival rate of between 10 to 15%(2). Survival appears to be slightly better in females but the younger age at diagnosis and the finding of less extensive disease at diagnosis in such patients may contribute to better survival.

## CONCLUSION

We presented our experience with 2 local Chinese patients, both females, with functioning adreno-cortical carcinomas. Our experience is evaluated against that of other centres with more extensive experience with this rare malignant condition. The life threatening hypotension and hypoglycaemia associated with aminoglutethimide usage was a hitherto unexpected situation and clinicians planning to embark upon this modality of treatment should be cognizant of this possible adverse outcome.

**REFERENCES**


1. Hutter AM Jr, Kayhoe DE: Adrenal cortical carcinoma: Clinical features of 138 patients. Am J Med 1966;41:572-80.
2. King DR, Lack EL: Adrena cortical carcinoma: A clinical and pathologic study of 49 cases. Cancer 1979;44:239-44.
3. Lipsett MB, Hertz R, Ross GT: Clinical and pathophysiologic aspects of adrenocortical carcinoma. Am J Med 1963;35:374.
4. Scott HW Jr, Foster JH, Rhamy JK, Klatte E, Liddle GW: Surgical management of adrenocortical tumours with Cushing's syndrome. Ann Surg 1971;173:892-905.
5. Hutter AM Jr, Kayhoe DE: Adrenal cortical carcinoma: Results of treatment with o,p'DDD in 138 patients. Am J Med 1966;41:581-92.
6. Hajjar RA, Hickey RC, Samaan NA: Adrenal cortical carcinoma: A study of 32 patients. Cancer 1975;35:549-54.
7. Hughes SWM, Burley DM: Aminoglutethimide: A "side effect" turned to therapeutic advantage. Postgrad Med Jour 1970;46:409-16.
8. Australian National Drug Information Service: Profile on aminoglutethimide 1983.
9. Misbin RI, Canary J, Willard D: Aminoglutethimide in the treatment of Cushing's syndrome. J Clin Pharm 1976:645-51.
10. Schteingart DE, Cash R and Conn JW: Aminoglutethimide and metastatic adrenal cancer. JAMA 1966;198:1007.