

Development of Ipsilateral Adrenocortical Carcinoma Sixteen Years after Resection of an Adrenal Tumour Causing Cushing's Syndrome

HS Tan,¹ MBBS, MRCP (UK), AC Thai,¹ M Med (Int Med), FAMS, FRCP (Edin), ME Nga,² MBBS, JJ Mukherjee,¹ MD, MRCP (UK), FAMS

Abstract

Introduction: At times, it may be difficult to differentiate early stage, low-grade adrenocortical carcinoma from benign adrenal adenoma. **Clinical Picture:** A 53-year-old lady underwent right adrenalectomy for a 4-cm adrenocortical tumour causing Cushing's syndrome. Histology revealed an adrenocortical adenoma. Sixteen years later, she presented with a 14-cm adrenal tumour, again on the right side. **Treatment:** She underwent surgical removal of the tumour. Histology confirmed adrenocortical carcinoma. **Outcome:** She died of metastatic disease 17 months later. **Conclusions:** This case highlights the importance of long-term, systematic follow-up of patients treated for benign adrenal adenomas, especially if the tumour size exceeds 4 cm.

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Key words: Adrenal cortex neoplasms, Adrenal gland hyperfunction, Neoplasm recurrence

Introduction

Adrenocortical carcinoma is a rare tumour, with an annual incidence of 0.5 to 2 per 1 million people. The overall 5-year survival rate ranges from 16% to 38%.¹⁻⁴ Recurrence, even after seemingly complete resection, is common, occurring in 23% to 85% of patients.^{3,5,6} The reported mean disease-free interval ranges from 1.2 years to 2.4 years.^{2,6} To the best of our knowledge, the longest reported interval to local recurrence following surgical resection of a non-functioning adrenocortical carcinoma has been 16 years.⁷ We describe a patient who presented with an ipsilateral adrenocortical carcinoma 16 years following adrenalectomy for a functioning right adrenal tumour that had resulted in Cushing's syndrome, and discuss its implications on the management of seemingly benign adrenal tumours in clinical practice.

Case Report

This 53-year-old lady, known to have diabetes for 3 years, presented in 1986 with an urinary tract infection, when it was noted that she had Cushingoid features. Blood pressure was normal at 130/80 mm Hg. Hormonal work-up revealed loss of diurnal variation of cortisol secretion (8 am and midnight cortisols being 523 nmol/L and 502 nmol/L respectively). Her serum cortisol levels failed to

suppress adequately during the low-dose (2-mg dexamethasone/day) and high-dose (8-mg dexamethasone/day) dexamethasone suppression tests. The baseline and 48-hour post dose serum cortisol levels were 523 nmol/L and 605 nmol/L respectively during the low-dose, and 500 nmol/L and 662 nmol/L respectively during the high-dose dexamethasone suppression tests.

Plasma corticotrophin (ACTH) levels were undetectable. Computed tomography (CT) of the abdomen revealed a 4-cm right adrenal tumour; the left adrenal gland was normal. She underwent right adrenalectomy via the posterior approach. Intraoperatively, a 4-cm adrenal tumour weighing 15.7 g was removed. Histology revealed mild nuclear pleomorphism, but no significant mitotic activity. There was no capsular or vascular invasion (Fig. 1). A diagnosis of benign adrenal adenoma was considered. Postoperatively, she required replacement doses of prednisolone, which was tapered and stopped 20 months after surgery, when a 250-mcg ACTH stimulation test showed an adequate peak serum cortisol level of 597 nmol/L at 60 minutes. Her diabetic control improved such that she was able to stop her diabetic medication without deterioration in her glycaemic control. She was subsequently lost to follow-up.

She presented 16 years later in 2002, aged 69 years, with complaints of lethargy, loss of appetite and weight loss over

¹ Department of Medicine

² Department of Pathology

National University Hospital, Singapore

Address for Reprints: Dr JJ Mukherjee, Department of Medicine, National University Hospital, 5 Lower Kent Ridge Road, Singapore 119074.

Email: jjmukh@nuh.com.sg

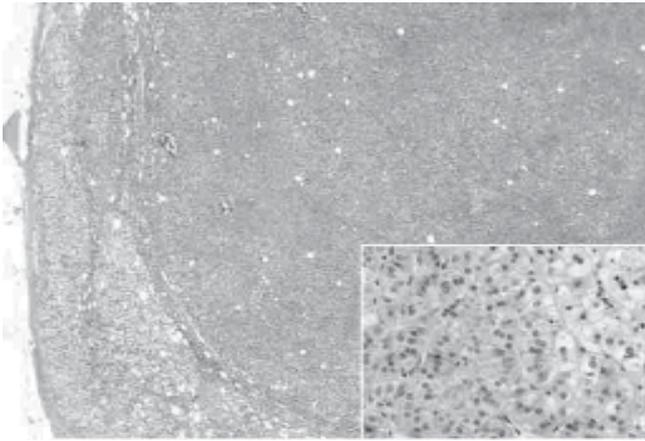


Fig. 1. Photomicrograph of the adrenal cortical adenoma resected in 1986, showing a lobulated appearance, without necrosis or fibrous bands. Inset: high power view showing the admixture of pale and eosinophilic cells. (Haematoxylin and eosin stain; 100x and 400x magnification)

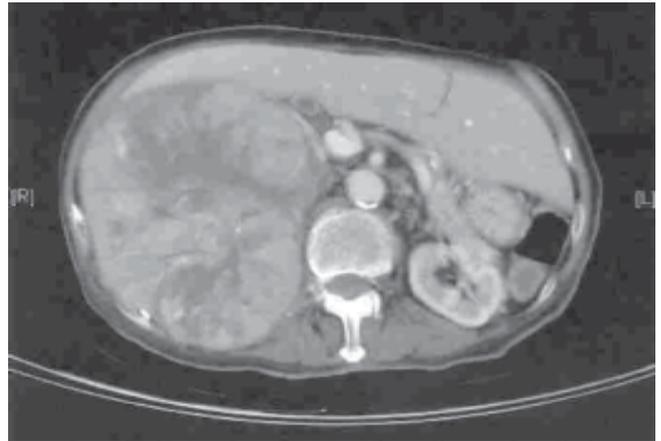


Fig. 2. CT scan of the abdomen, showing a huge mass measuring 14 x 12 cm, arising in the region of the right adrenal bed. The mass has a heterogeneous appearance with solid areas that show contrast enhancement and prominent hypodense areas consistent with necrosis.

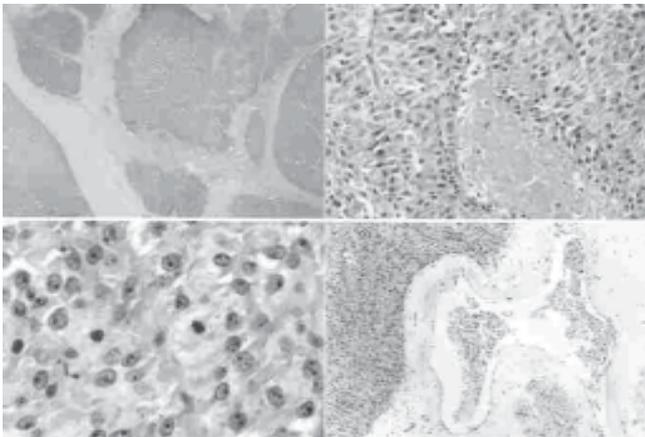


Fig. 3. Photomicrograph of the adrenal cortical carcinoma resected in 2002. Clockwise from top left: (i) Low power view showing nodules separated by dense fibrous bands; (ii) Focus of coagulative necrosis; (iii) Intravascular tumour spread; (iv) High power view showing a mitotic figure and moderate nuclear pleomorphism. (Haematoxylin and eosin stain; 40x, 200x and 100x and 400x magnification respectively).

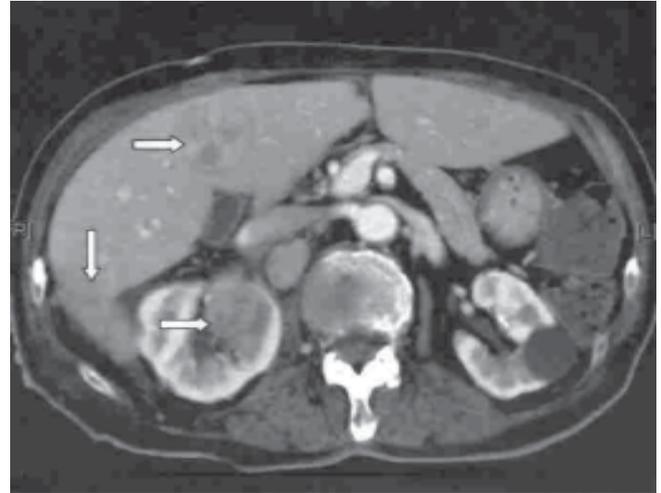


Fig. 4. Repeat CT scan of the abdomen, done 1 year after surgical resection, showing metastatic lesions (white arrows) in the liver and the right kidney.

the last 6 months. She had undergone coronary artery bypass grafting in 1998. On examination, she did not have a Cushingoid appearance. Blood pressure was 130/70 mm Hg. Abdominal examination revealed a palpable mass over the right flank. CT scan of the abdomen (Fig. 2) revealed a 14-cm mass in the region of the right adrenal bed. The lesion was heterogeneous in appearance, with solid areas that enhanced with contrast as well as prominent hypodense areas likely to represent necrosis. Chest X-ray was normal. The 24-hour urine free catecholamine and metanephrine excretion was normal. However, the 24-hour urine free cortisol excretion was mildly elevated at 495 nmol/day (normal 59 nmol/day to 413 nmol/day; urine volume 854 mL). She underwent laparotomy, whereby a 17-cm right adrenal tumour, weighing 1.2 kg, was removed, together with 2 lymph nodes that were situated anterior to the

inferior vena cava. There was no intraoperative evidence of liver metastases. Histology revealed cords and trabeculae of polygonal cells with abundant eosinophilic cytoplasm that stained positively for synaptophysin. Staining for alpha-fetoprotein, vimentin, chromogranin, neurofilament and epithelial membrane antigen were all negative. The tumour showed moderate nuclear atypia with many nuclei harbouring prominent nucleoli (Fig. 3). Mitoses were not prominent but were greater than those seen in the tumour resected in 1986, approaching 5 per 50 high power fields. In some areas, there was prominent necrosis and the tumour was divided by broad fibrous bands, which gave it a nodular appearance. In addition, there was tumour extension to the capsular surface as well as vascular space involvement. An anterior vena caval lymph node was almost completely replaced by metastatic tumour, further confirming the diagnosis of adrenocortical

carcinoma.

Postoperatively, she made an uneventful recovery. A 250-mcg ACTH stimulation test revealed an inadequate rise in serum cortisol level from a baseline value of 281 nmol/L to a peak of 368 nmol/L. She was hence discharged with oral hydrocortisone 10 mg in the morning and 5 mg in the evening. When reviewed 5 months later, she was well, with no clinical evidence of recurrence or metastatic disease. A CT scan of the abdomen did not reveal any evidence of recurrent disease. A repeat 250-mcg ACTH stimulation test continued to reveal suboptimal cortisol response, with the serum cortisol level rising to a peak of 250 nmol/L at 60 minutes. Hydrocortisone replacement was continued.

When reviewed a year later, she was clinically asymptomatic. However, a follow-up CT scan of the abdomen revealed a recurrence of the tumour in the right adrenal bed with local spread to the right kidney as well as multiple hepatic and pulmonary metastases (Fig. 4). CT-guided fine needle aspiration of the recurrent mass in the adrenal bed confirmed adrenocortical carcinoma. 24-hour urine free cortisol excretion was normal at 295 nmol/day. No surgical intervention or chemotherapy was offered in a relatively asymptomatic patient. However, her condition gradually deteriorated and she expired 5 months later, 17 months following the second laparotomy, and 17 years following her first presentation in 1986.

Discussion

Cushing's syndrome is the most common presentation amongst all hormonally active adrenocortical carcinomas, being reported in 30% of such patients.⁴ Our patient had initially presented with Cushing's syndrome due to a right adrenal tumour, which was cured following right adrenalectomy, necessitating glucocorticoid replacement for 20 months. A diagnosis of a benign adrenocortical adenoma was then considered in light of the histology report.

However, she developed an adrenocortical carcinoma at the same site 16 years later. This could be the result of the development of a new tumour in residual normal adrenal tissue inadvertently left behind during the first laparotomy, a very rare occurrence, or an adrenal cortical carcinoma arising in adrenal rests present in the vicinity of the previously removed adrenal gland. The possibility of recurrence of a slow-growing adrenocortical carcinoma that was initially erroneously considered to be a benign adrenocortical adenoma is another consideration. Histopathologic review of the 4-cm tumour removed in 1986 concurred with the initial opinion of a benign adrenocortical adenoma. However, differentiating between an early-stage adrenocortical carcinoma and a benign adrenocortical adenoma is often difficult based on histopathological

features alone.⁸ In retrospect, despite the histological features, the initial tumour could have been a low-grade, slow-growing adrenocortical carcinoma that resulted in recurrent disease 16 years later. Indeed, the tumour excised 16 years later also had a very low mitotic rate, reminiscent of the earlier lesion. However, it now demonstrated the aggressive features of an adrenocortical carcinoma of large size, capsular and vascular invasion, necrosis, rapid growth and metastases within a 1-year period. Some authors have suggested that adrenal carcinoma can arise as a result of progression through hyperplasia to adenoma to carcinoma, but definite proof is lacking and the pathogenesis of adrenocortical carcinoma remains poorly understood.⁹

It has been well described that the risk of malignancy in an adrenal tumour increases with increasing tumour size and a recent study reported that a tumour size of 4 cm confers a sensitivity and specificity of 93% and 42% respectively for diagnosing malignancy.¹⁰ However, adrenal size alone cannot be used to differentiate between benign and malignant adrenal tumours. Adrenocortical carcinomas represent 2% of all adrenal tumours ≤ 4 cm in diameter, 6% of tumours from 4.1 cm to 6 cm in diameter and 25% of all tumours > 6 cm in diameter. On the other hand, benign adrenocortical adenomas comprise 18% of adrenal tumours > 6 cm in diameter and 65% of masses ≤ 4 cm in diameter.¹¹

Late recurrences of adrenocortical carcinoma are rare, with only a handful of reported cases. Mufti and Farrell⁷ reported the longest disease-free interval to local recurrence in a patient with a non-functioning left adrenocortical carcinoma. The 69-year-old lady described in their report had a recurrence of adrenocortical carcinoma 16 years after surgical adrenalectomy. To the best of our knowledge, our patient is the first reported case of an adrenocortical carcinoma developing 16 years following the surgical excision of a functioning adrenal tumour.

Conclusion

Our case highlights the diagnostic difficulty in differentiating between an adrenocortical carcinoma and a benign adrenal adenoma in the absence of capsular or vascular invasion or documented metastases. The two can be distinguished from each other by certain differences, including tumour size and certain radiological characteristics, such as irregular margins, inhomogeneous density with marked contrast enhancement and the presence of necrosis, haemorrhage or calcification. Histopathological examination can also be helpful, but definitive classification can be difficult, if not impossible, in the absence of capsular, vascular or lymphatic invasion. Patients with adrenal adenomas measuring > 4 cm in diameter should undergo systematic long-term surveillance with periodic imaging and hormonal evaluation so that timely intervention can be

carried out should they indeed have a slow-growing adrenocortical carcinoma. This may improve the overall mortality rate of this dreadful disease.

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