



CASE REPORT

CUSHING'S SYNDROME CAUSED BY ECTOPIC ACTH SECRETION FROM PULMONARY TUMOURLETS

F J Pirie, A A Motala, A Amod, R Chetty, S R Thomson, S Lalloo, M A K Omar

Ectopic adrenocorticotrophic hormone (ACTH) secretion accounts for 9 - 18% of all causes of Cushing's syndrome.<sup>1</sup> The commonest source of the ectopic ACTH syndrome is carcinoma of the lung, with a smaller contribution from carcinoid tumours. While bronchial carcinoid tumours are reported to be responsible for 5 - 39% of ectopic ACTH-associated Cushing's syndrome, pulmonary tumourlets, which represent an uncommon form of neuroendocrine proliferation, may rarely give rise to Cushing's syndrome by secreting ACTH.<sup>1,2</sup> This report details the identification of two such cases presenting to the Endocrine Unit at King Edward VIII Hospital, Durban, South Africa.

CASE 1

A 38-year-old woman was referred to King Edward VIII Hospital from a rural area in August 1993 for management of Cushing's syndrome. She gave a history of weight gain and mood changes of 3 months' duration. There was no menstrual irregularity and no respiratory symptoms were reported. The referring hospital noted that she had a Cushingoid habitus and was hypertensive. Physical examination confirmed features typical of Cushing's syndrome associated with severe hypertension, with no evidence of end-organ damage. There was inadequate serum cortisol suppression with the standard low-dose dexamethasone suppression test (serum cortisol 390 nmol/l after dexamethasone 0.5 mg 6-hourly for 48 hours), and midnight serum cortisol was 802 nmol/l with corresponding plasma ACTH 60 pg/ml, indicating ACTH-mediated hypercortisolaemia with no circadian variation.

Department of Medicine, University of Natal, Durban  
F J Pirie, FCP (SA), MD  
A A Motala, FRCP, MD  
A Amod, MB ChB, FCP (SA)  
M A K Omar, FRCP, FCP (SA), MD

Department of Anatomical Pathology, University of Natal, Durban  
R Chetty, MB ChB, FRCPath

Department of Surgery, University of Natal, Durban  
S R Thomson, ChM, FRCS (Edin & Eng)

Department of Radiology, University of Natal, Durban  
S Lalloo, MB ChB, FCRad (SA)

Serum cortisol fell to 183 nmol/l after the high-dose 48-hour dexamethasone suppression test. A magnetic resonance image (MRI) scan of the pituitary revealed a right-sided microadenoma. On the basis of the suppression achieved with the high-dose dexamethasone suppression test and the demonstration of a pituitary lesion, a trans-sphenoidal procedure was undertaken in December 1993. The surgeon failed to locate the adenoma and the tissue submitted for histological examination revealed normal pituitary tissue. A second attempt to resect the lesion was undertaken in September 1994 through a right fronto-temporal craniotomy. Postoperatively generalised seizures occurred, requiring chronic therapy with phenytoin, and pituitary insufficiency ensued, requiring therapy with desmopressin, levothyroxine and cyclical oestrogen and progesterone. The clinical features of Cushing's syndrome persisted.

In June 1995 a chest radiograph showed bilateral fine nodular opacities of mid- and lower zonal distribution suggestive of miliary tuberculosis. Tuberculosis chemotherapy was commenced. In January 1996, midnight serum cortisol and plasma ACTH measured 798 nmol/l and 70.2 pg/ml respectively. Repeat chest radiograph remained unchanged, despite tuberculostatic therapy. High resolution computed tomography scan (Philips Tomoscan LX) demonstrated multiple non-calcified nodules 2 - 10 mm in size in a random distribution within the mid- and lower zones of both lungs (Fig. 1). While most nodules were discrete, the largest demonstrated marginal spiculation and pleural tags (Fig. 1). These findings were considered to represent peribronchiolar fibrosis. The differential diagnosis for these HRCT findings included granulomatous disorders (including tuberculosis and sarcoidosis), metastatic tumour deposits and lymphoma. There were no respiratory symptoms. A transbronchial lung biopsy

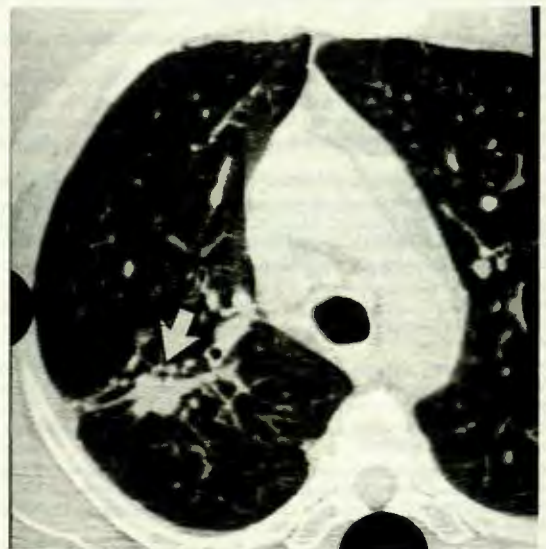


Fig. 1. HRCT scan demonstrating pulmonary nodule (arrow) with spiculation and pleural tag.



revealed nonspecific chronic inflammation and octreotide scintigraphy failed to demonstrate any areas of abnormal uptake. A repeat high-dose dexamethasone suppression test demonstrated lack of suppression (baseline serum cortisol 48 nmol/l, post-test serum cortisol 658 nmol/l). An open lung biopsy was performed in June 1998. The resected specimen demonstrated multiple carcinoid tumourlets with positive ACTH immunostaining. The lesions were too widespread for resection and bilateral adrenalectomy was offered. The patient declined any further surgical intervention and was given itraconazole. Following admission to hospital with acute otitis media in September 1999, the patient died suddenly of an unknown cause. The family refused permission to perform a postmortem examination.

## CASE 2

A 17-year-old male patient was referred in August 1997 with a diagnosis of cyclical Cushing's syndrome. He had originally presented to a paediatrician at the age of 11 years with recurrent nephrolithiasis and weight gain. A diagnosis of Cushing's syndrome was made (the details of which were not available to this unit), but spontaneous clinical and biochemical remission occurred before completion of the diagnostic evaluation. During the following 5 years four clinical relapses and spontaneous remissions occurred, each episode self-treated briefly with bromocriptine. In 1997, the clinical signs failed to regress with bromocriptine therapy, effort-induced dyspnoea developed and frequent episodes of nephrolithiasis occurred, requiring extra-corporeal shock wave lithotripsy on two occasions. ACTH-dependent Cushing's syndrome was demonstrated, with plasma ACTH 75 pg/ml. There was failure of serum cortisol suppression with the 8 mg overnight dexamethasone suppression test. Computed tomography (CT) scan of the pituitary revealed a left-sided microadenoma. Inferior petrosal venous sinus sampling failed to demonstrate a central/peripheral ACTH gradient and octreotide scintigraphy failed to show any abnormal areas. In August 1997, 24-hour urine 5-hydroxyindole-acetic acid excretion measured 52  $\mu\text{mol}$  (normal < 50  $\mu\text{mol}$  per 24 hour). The patient defaulted further follow-up until late 1998. On re-evaluation, a chest radiograph showed bilateral pulmonary nodules of varying size, with predominant involvement of the left base. This was interpreted as bronchiectasis with mucous plugs. An HRCT scan of the chest revealed bilateral non-calcified nodules 2 - 20 mm in size in a distinct peribronchiolar distribution, with clustering in parts (Fig. 2). An open lung biopsy was performed in January 1999 and histological examination revealed multiple nodules of carcinoid tumour cells in cords and sheets, with positive ACTH immunostaining. As with the first patient, the lesions were too widespread for resection. In March 1999, bilateral adrenalectomy and ureterolithotomy were performed via an anterior approach as a combined single stage procedure. Both

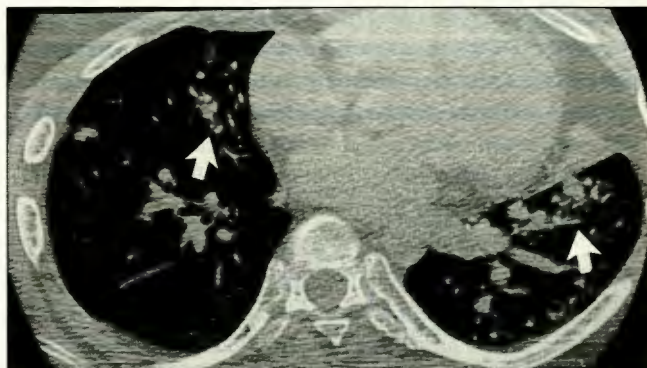


Fig. 2. HRCT scan demonstrating peribronchiolar distribution of nodules with clustering (arrows).

adrenal glands revealed histological evidence of adrenocortical hyperplasia. The postoperative period was complicated by partial septal wound dehiscence from a right peri-ureteric abscess that developed as a result of persistent urine leak from the ureterolithotomy. This required formal retroperitoneal drainage and prolonged ureteric stenting. At present the patient is asymptomatic, on glucocorticoid and mineralocorticoid replacement therapy.

## DISCUSSION

Both patients manifested a highly unusual form of ectopic ACTH-associated Cushing's syndrome. In both cases periodicity of secretion was noted biochemically, and to a lesser extent clinically. Furthermore, in both patients pituitary imaging was misleading (incidentally identifying non-functional pituitary adenomas); in the first case, the associated finding of suppression of serum cortisol after administration of high-dose dexamethasone resulted in inappropriate hypophysectomy. Incidental detection of pituitary adenomata have been reported in 27% of postmortem examinations<sup>3</sup> and 10% of subjects in the 30 - 40-year age group on MRI.<sup>4</sup> The clinical significance of a pituitary adenoma, detected with MRI scanning, must therefore be interpreted in conjunction with the biochemical data to avoid false-positives, as in the cases reported here. There is no way of discriminating between an incidental adenoma and an actively secreting pituitary lesion using current imaging techniques. Periodic release of ACTH by benign extra-pituitary tumours has been previously reported.<sup>1</sup> These tumours may retain partial sensitivity to feedback inhibition by high doses of exogenous glucocorticosteroids and thus mimic pituitary ACTH-secreting adenomas.<sup>5</sup> Both cases demonstrated periods during which suppression of serum cortisol was achieved with high-dose dexamethasone, as well as periods of failed suppression. This was possibly owing to partial ACTH sensitivity or periodicity of ACTH secretion. This observation highlights the need for definitive demonstration of the ACTH source before surgical intervention.



Corticotrophin-releasing hormone (CRH) stimulation tests were not done in either case because of the non-availability of this pituitary secretagogue at this institute. The CRH test is used as a means of differentiating eutopic from ectopic ACTH secretion, based on the principle that corticotroph adenomas express CRH receptors in greater numbers than ectopic ACTH sources.<sup>6</sup> It is probable that the test would have assisted in identifying an ectopic ACTH source, although this is speculative. The National Institutes of Health (NIH) study on the clinical utility of the CRH test reported a sensitivity of 93% and specificity of 100% in discriminating pituitary from ectopic ACTH sources (including 13 cases of carcinoid tumours). The criterion used was a mean plasma ACTH increment of 35% above the basal value at 15 and 30 minutes after the injection as being indicative of a pituitary ACTH source. Mean serum cortisol increments of 20% or more above the basal level at 30 and 45 minutes resulted in a sensitivity of 91% and specificity of 88% in the same NIH study.<sup>7</sup> There were no cases of pulmonary tumourlets in this study and in the case of pulmonary tumourlets reported by Arioglu and colleagues<sup>2</sup> from the same centre, CRH testing was not performed.

In both cases abnormal chest radiographs were present for a number of years before the diagnoses were established. The radiographs were misinterpreted as miliary tuberculosis in the first patient and bronchiectasis with mucous plugs in the second patient. Both of these conditions are seen with great frequency in this environment. Neither patient had significant respiratory symptoms with effort, nor were any auscultatory abnormalities evident, therefore indicating slow growth of the pulmonary lesions. Pulmonary tumourlets are generally located in the bronchiolar mucosa and submucosa<sup>8</sup> and this anatomical siting is probably responsible for the silent nature of the lesions in most cases. The release of neuropeptides is thought to mediate the development of peribronchiolar fibrosis, as was seen on the HRCT scan in case 1.<sup>9</sup> The natural history of pulmonary tumourlets is not well documented in view of the relatively few cases that have been described. Malignant transformation has, however, been documented in at least one previous report.<sup>10</sup>

Much of the literature pertaining to bronchopulmonary carcinoid secretion of ectopic ACTH is related to discrete neoplasms, rather than the diffuse tumourlets observed in these two cases.<sup>1</sup> Pulmonary tumourlets have an obscure origin and have been considered to reflect uncontrolled hyperplasia of neuroendocrine tissue that is normally found in the bronchiolar mucosa of the adult lung.<sup>2,11</sup> Stimuli for the exuberant growth of this tissue to the extent witnessed in these two cases are not known. In other situations a history of cigarette smoking has been associated with pulmonary neuroendocrine cell hyperplasia, although to a lesser degree than in the two cases reported here.<sup>12</sup> The two patients differed in terms of age, ethnicity and geographical location and it

would therefore be difficult to implicate a common environmental precipitant. It is possible that pulmonary tumourlets and carcinoid tumours represent a continuum of pulmonary neuroendocrine cell growth, although genotypic differences between the cells of each of these conditions have been described, implying that the two conditions may be separate disorders.<sup>8</sup>

In conclusion, two cases of Cushing's syndrome caused by ectopic ACTH secretion from pulmonary tumourlets are described, with both cases demonstrating periodicity of hormone secretion and dexamethasone responsiveness, with minimal clinical evidence of pulmonary disease. Both cases illustrate the necessity of following a structured algorithm of clinical and laboratory evaluation in patients with Cushing's syndrome before embarking on surgical intervention.

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