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Ectopic Cushing's Syndrome In A Young Female With A Typical Bronchial Carcinoid Tumour

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ABSTRACT

A 17-year-old female with a large mass in the left thorax presenting with ectopic Cushing's syndrome is described. Biochemical evaluation revealed a corticotropin(ACTH)-dependent hypercortisol state. Surgical resection of the tumour resulted in clinical remission and correction of hypercortisolism and normal plasma ACTH levels. The histology was that of an atypical carcinoid. Bronchial carcinoid tumour is an extremely uncommon but well recognised cause of ectopic Cushing's syndrome. These patients may pose diagnostic dilemma in distinguishing from those with Cushing's disease because of the similarity in the clinical, biochemical and radiologic findings.

Keywords: hypercortisolism, ACTH, neuroendocrine tumour, diagnosis, evaluation.

INTRODUCTION

The association of a bronchial carcinoid as a source of ectopic ACTH secretion has been reported since 1957[1], with approximately 70 cases in the literature to date[2]. These patients are often young, with radiologically occult tumour and long duration of Cushing's syndrome. They may be indistinguishable from those with ACTH producing pituitary tumour or Cushing's disease in terms of clinical, biochemical and radiologic features[3-5]. We report an unusual case of ectopic Cushing's syndrome caused by an atypical bronchial carcinoid which is of massive size and with a rapid tempo of clinical manifestation in a young female patient. We discussed the diagnostic evaluation with emphasis on potential pitfalls.

CASE REPORT

SSY, a 17-year-old student was seen by her physician in her home town with complaints of intermittent bifrontal headache, generalised weakness with difficulty in climbing stairs, and polyphagia with weight gain for 3-4 months' duration. There was no vomiting, visual obscuration, or diplopia associated with the headache. There were no other constitutional symptoms except for occasional dull aching pain over the left lower chest wall and interruption of menstrual flow for the past 3 months.

She was found to be cushingnoid clinically with facial plethora, widespread acne, purpuric striae, central obesity and proximal myopathy. Blood pressure was 150/90 mmHg. The biochemical investigations done were as follows: serum potassium 2.7 mmol/L, serum sodium 142 mmol/L, serum chloride 101 mmol/L, serum bicarbonate 18.8 mmol/L, random serum cortisol at 1.30pm 840 nmol/L, and morning plasma ACTH 634 ng/L. A computed tomography(CT) of the pituitary was reported to be compatible with pituitary microadenoma. Abdominal CT was normal and both adrenals were of normal size and configuration. The patient was diagnosed to have Cushing's disease and a neurosurgical referral was recommended.

However the family decided to have a second opinion at this hospital. A systemic review did not yield additional information and there were no complaints of dyspnoea, wheeze, or gastro-intestinal symptoms. Apart from the findings of Cushing's syndrome, there was increased pigmentation at the nail bases of the fingers and toes. Her blood pressure was 150/100 mmHg.

Laboratory investigations including haematological indices, blood urea nitrogen and electrolytes were all normal. Biochemical evidence of hypercortisolism was established with a 24-hour urinary cortisol value of 2.42 µmol/day(0.22-0.40). The corresponding urinary cortisol values evaluated on the second day of the low-dose and high-dose dexamethasone suppression tests(DST) were 4.52 µmol/day and 3.31µmol/day respectively, showing a complete lack of suppression in both tests. A 9am plasma ACTH level was elevated at 168.7 ng/L (10-40), indicating ACTH-dependent hypercortisolism.

The chest roentgenogram revealed a large, rounded opacity of fairly homogeneous composition in the left lower zone with obliteration of the left cardiac border and extending to the chest wall (Fig 1a). This corresponded to the thoracic CT findings of a large necrotic mass in the mid and lower zones of the left lung. There were no radiological evidence of hilar or mediastinal lymphadenopathy, or the invasion of adjacent structures(Fig 1b). Magnetic resonance imaging(MRI) of the pituitary did not show the presence of microadenoma or any other abnormality.

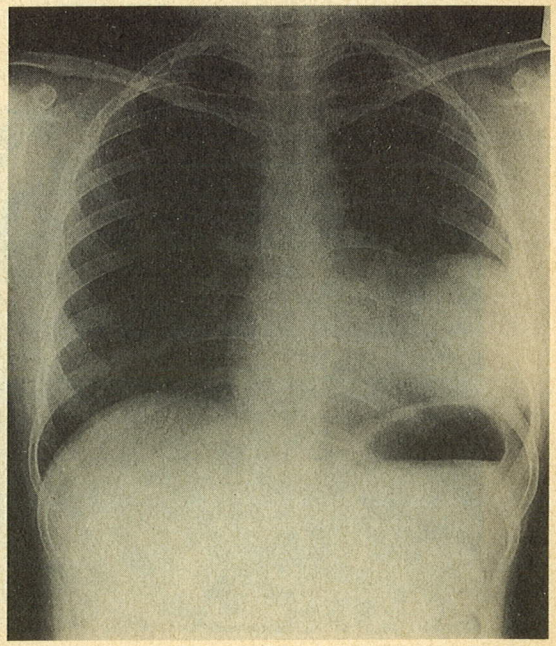

Fig 1a - Chest radiograph showing a large rounded opacity in the left lower zone.

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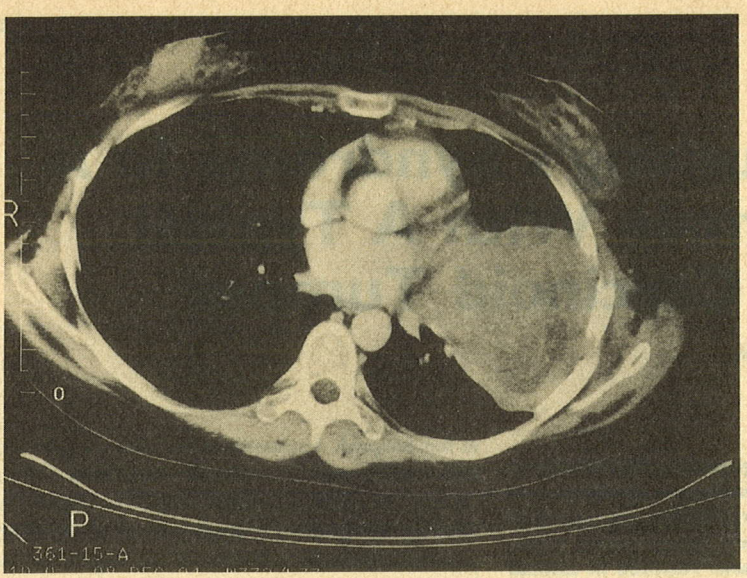

Fig 1b - CT showing a well-defined necrotic mass in the left hemithorax with no evidence of mediastinal invasion or lymphadenopathy.

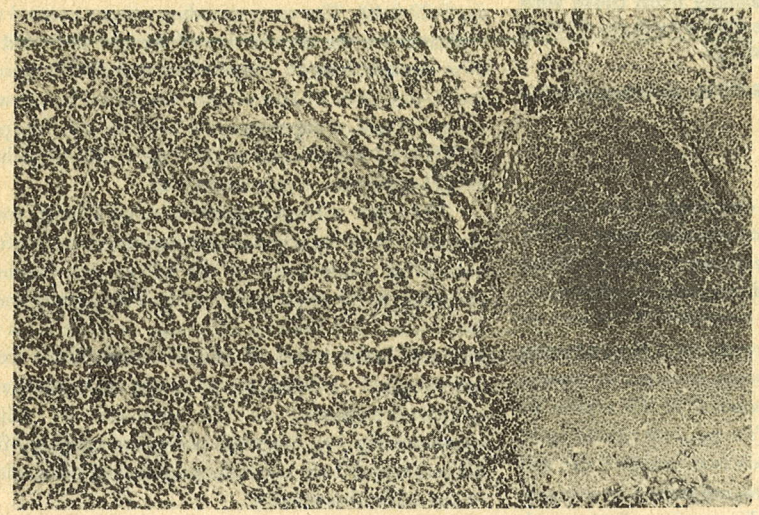

Fig 2a - Photomicrograph of atypical carcinoid showing small tumour cells with dark nuclei which are arranged in nests separated by fibrovascular septa. A large area of necrosis is seen on the left portion. (H&E, X100)

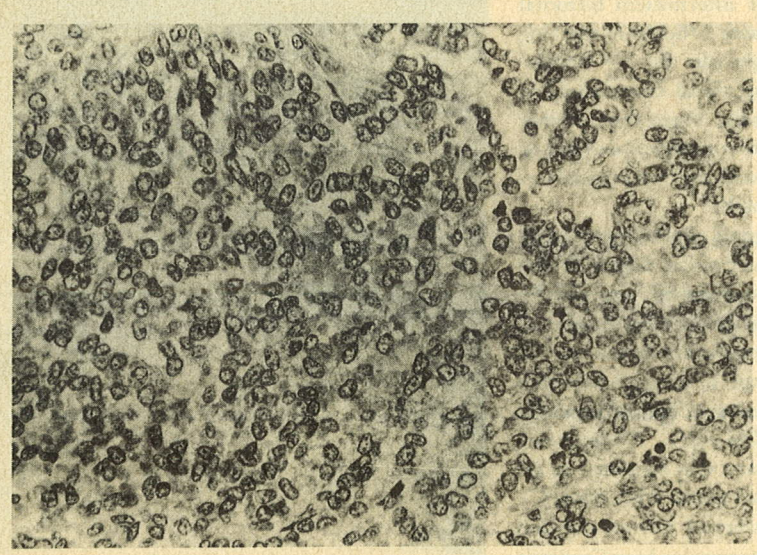

Fig 2b - Atypical carcinoid with tumour cells showing cytoplasmic immunostaining for ACTH. (Immunoperoxidase stain, X400)

The serum alpha-foetoprotein and beta-HCG levels were 2.6 ug/L (1.0-10.0) and non-detectable respectively. The 24-hour urinary 5-hydroxy indole acetic acid(5-HIAA) excretion was 19.5 µmol/day(0-52). The patient had a percutaneous core biopsy of the thoracic mass lesion which revealed features of neuroendocrine carcinoma of the non small-cell type. A metastatic workout including CT studies of the brain and abdomen, and ^{99m}Technetium DPD whole body skeletal scintigraphy were all negative. A bronchoscopic evaluation was normal up to the segmental bronchi and a thoracotomy was done on 20 December 1994. Intraoperatively, a well circumscribed 8cm x 8cm x 8cm necrotic tumour was found in the oblique fissure with close adherence to the lingula. There were no mediastinal invasion or enlarged hilar or mediastinal lymph nodes. The tumour was excised completely with the attached lingula. The histopathology report was that of an atypical bronchial carcinoid with large areas of necrosis and haemorrhage. Frequent mitoses were noted and the tumour cells showed focal positivity for ACTH (Fig 2a and b).

The plasma ACTH levels declined to 14.6 ng/L and 8.46 ng/L on the first and second post-operative days respectively. An Indium-111 labelled pentatreotide whole body scintigraphy was done post-operatively and this did not show any abnormal uptake. The patient has remarkable resolution of the cushingnoid features with complete normalisation of the blood pressure when reviewed three months post-operatively.

DISCUSSION

Bronchial carcinoid tumours constitute approximately 5% of all primary lung cancers[3]. They are classified as a type of neuroendocrine neoplasm and they have the potential to secrete a variety of hormones and chemical substances found in both the central nervous system and the epithelial cells of numerous organs. These tumours are usually slow growing and of low grade malignancy[3,5]. Atypical carcinoid are higher grade neoplasms with higher incidence of nodal and distant metastasis[6]. At the extreme end of the spectrum of bronchopulmonary neuroendocrine tumours are the highly malignant small-cell lung cancers.

The diagnostic approach here involve several phases: the confirmation of hypercortisolism, the differentiation between ACTH-dependent and ACTH-independent Cushing's syndrome, the differentiation between pituitary and ectopic sources of the ACTH-dependent Cushing's syndrome, and the localisation of the tumour for definitive surgery. The distinction between an ACTH-producing pituitary microadenoma and an occult ectopic ACTH-secreting tumour poses the greatest challenge in these aspects.

Hypercortisolism can be established biochemically with the measurement of free cortisol in a 24-hour urine specimen and/or an overnight 1 mg dexamethasone suppression test[7]. The diagnosis of Cushing's syndrome may be confirmed in those with hypercortisolism by performing the 2-day low dose DST[8,9]. This is necessary only in those with mild hypercortisolism and pseudo-Cushing's states cannot be excluded[10]. In our patient, the diagnosis of Cushing's syndrome was not adequately established during her first consultation as only a random serum cortisol level was measured, although in this instance it was later supported by a significantly elevated plasma ACTH.

The next step involves measuring plasma ACTH level to differentiate between ACTH-dependent and ACTH-independent Cushing's syndrome. It is a useful guide that plasma ACTH >200 ng/L points towards an ectopic origin while pituitary cases have inappropriately normal or mildly

elevated ACTH levels. There is however significant overlap with one-third of ectopic cases having levels <200 ng/L. Conversely, patients with adrenal tumours have suppressed ACTH levels. The markedly elevated plasma ACTH level and clinical evidence of hyperpigmentation noted in our patient belies an ectopic aetiology.

Having established an ACTH-dependent state, the differentiation between pituitary and ectopic causes can be enhanced by several biochemical tests before imaging modalities are employed for anatomical localisation of the tumour. The 2-day high dose DST[8,11] or the modified overnight high dose DST[12], is most useful in this regard. Patients with Cushing's disease retain certain degree of negative feedback inhibition of pituitary ACTH release by elevated plasma cortisol, and hence the cortisol secretion is characteristically suppressible with high dose DST. Although the cortisol secretion is classically non suppressible with high dose DST in ectopic cases, there is significant overlap with variable suppression especially in ectopic Cushing's syndrome arising from carcinoid tumours. Other diagnostic tests include the corticotropin-releasing hormone (CRH) stimulation test and the less desirable metyrapone test[13,14]. Our patient showed a complete lack of suppression with high dose DST which is consistent with an ectopic aetiology.

Imaging modalities used for anatomical localisation of suspected endocrine tumour should not precede the biochemical differentiation of the functional abnormality of the target glands concerned. The injudicious use of diagnostic imaging may pose further diagnostic dilemma as illustrated by our case. MRI of the pituitary offers the best imaging tool if Cushing's disease is suspected based on clinical and biochemical findings. In equivocal cases and in those with negative imaging results, bilateral inferior petrosal sinus sampling(BIPPS) may be helpful for differentiation although false positive results may be obtained in an ectopic tumour with episodic secretion or one that secretes corticotrophin releasing hormone(CRH)[4]. In cases where ectopic Cushing's syndrome is suspected as in our patient, a chest roentgenogram followed by thoracic CT should be done as most of these tumours are intrathoracic in location. Our patient had an unusually large tumour and was spared the diagnostic difficulty that often accompanied those with occult tumours. The use of somatostatin analog whole body scintigraphy may prove useful in future as most neuroendocrine tumours are associated with functional somatostatin receptors[15].

Fewer than 5% of all patients with bronchial carcinoids manifest carcinoid syndrome. Large and central tumours may produce local manifestations such as cough, haemoptysis, pleuritic pain or infection[3]. Because these tumours are relatively slow growing, the symptoms may be tenuous and often disregarded as in our case. Therefore, screening patients for serotonin metabolites, such as 5-HIAA in blood or urinary specimens, as illustrated by our case, has limited value unless carcinoid syndrome is present.

Surgical resection is the definitive treatment with potential for cure in non-metastatic bronchial carcinoid tumour although recurrence may show up years or decades later[2,3,16]. The postoperative normalisation of plasma ACTH level as in our patient serves as an indicator of successful surgical resection. The 5-year survival rate for patients with typical and node-negative carcinoid tumours is >90% while this is reduced to 57% for those with atypical histology[17].

CONCLUSION

Bronchial carcinoid tumours are interesting neuroendocrine neoplasms which have the potential to secrete a host of neuroendocrine products and they must be considered in the differential diagnosis of any paraneoplastic syndrome. Our case of a young female presenting with Cushing's syndrome offers a challenging and stimulating diagnostic exercise. Despite the many possible diagnostic dilemmas that one may encounter in the management of such neoplasms, a careful and systematic approach often reaps rewarding and satisfying results as illustrated by our case.

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