Ectopic release of GHRH and ACTH from an adenoid cystic carcinoma resulting in acromegaly and complicated by pituitary infarction

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Summary: A 23 year old man presented with a tumour mass in the lung. Subsequent investigation showed ectopic secretion of adrenocorticotrophic hormone (ACTH) and growth hormone releasing hormone (GHRH) from an adenoid cystic carcinoma. The patient progressed to show the clinical effects of long term exposure to high blood levels of both growth hormone and cortisol. The case was complicated by pituitary infarction. The very high blood levels of ACTH, growth hormone (GH) and GHRH proved resistant to treatment with the somatostatin analogue, SMS 201-995, and a possible side effect of the drug is reported. To our knowledge this is the first reported case of ectopic hormone secretion by an adenoid cystic carcinoma.

Introduction

Acromegaly due to ectopic production of growth hormone releasing hormone (GHRH) has been described in association with a variety of tumours including carcinoid and pancreatic islet cell tumours.^{1,2,3,4} More than one ectopic hormone may be present in the tumour; in one reported case of metastatic carcinoid presenting clinically with acromegaly, gigantism and Cushing's syndrome,¹ for example, both growth hormone (GH) and GHRH were identified in the tumour. However, the presence of immunoreactive hormone in tumour tissue is not necessarily synonymous with ectopic hormone secretion; in one case of metastatic carcinoid, growth hormone was present in the tumour but no arteriovenous gradient was demonstrated across it.⁵ We report a case of ectopic secretion of GHRH and adrenocorticotrophic hormone (ACTH) from an adenoid cystic carcinoma with failure to respond to the somatostatin analogue SMS-201-995 (Sandoz). The case was further complicated by pituitary infarction. To our knowledge this is the first reported case of ectopic secretion by adenoid cystic carcinoma.

Case report

A 23 year old Caucasian man with no previous relevant medical history presented in June 1981 with pain in the right side of the chest and breathlessness. Chest X-ray showed a shadow in the right lung which was thought to have features of a dermatoteratoma. The patient refused further investigation, returning two years later in June 1983 complaining of a lump in the right side of the neck which had been present for some 8 months. Biopsy of the neck lump showed an adenoid cystic carcinoma which was presumed to be metastatic from the lung primary. Computed tomographic (CT) scan showed a large tumour mass in the right lung, and at thoracotomy an extensive non-resectable mediastinal mass was found. Treatment was commenced with radiotherapy to the chest and right side of the neck. In October 1983 the patient was admitted to St. Luke's Hospital, Guildford for chemotherapy. The patient was started on the Price-Hill chemotherapy regime (intermittent courses of vincristine, bleomycin, methotrexate and 5 fluoro-uracil). On admission, features of acromegaly were noted but no specific investigations were performed. The patient received seven cycles of chemotherapy finishing May 1984.

In July 1984 the patient was re-admitted complaining of thirst, polyuria, lethargy, unsteadiness of gait and bilateral swelling of both legs from foot to mid-calf. On examination, acne

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vulgaris, bilateral exophthalmos and skin pigmentation were noted. Marked proximal muscle wasting was present in all four limbs. The strong clinical features of acromegaly were supported by radiological measurement.

Some initial biochemical investigations are shown in Table I. Plasma cortisol levels which were high with no diurnal variation and no response to either low dose (2 mg overnight) or high dose (2 mg four times daily for 4 days) dexamethasone. Standard luteinising hormone releasing hormone (LHRH) and thyrotrophin releasing hormone (TRH) tests were performed; the results are shown in Table II. Basal testosterone was low and there was an exaggerated luteinising hormone (LH) response to LHRH. Although prolactin levels were markedly raised they subsequently fluctuated between 320 and 460 m U/l during a 6 hour saline infusion. Plasma GH levels – which were lower than on previous

occasions when they had been measured – rose in response to TRH/LHRH. Plasma thyroxine levels and the thyroid stimulating hormone (TSH) response to TRH were normal.

Hyperglycaemia persisted and the patient's diabetes which, in view of the high basal C-peptide levels appeared to be due to insulin resistance rather than to pancreatic failure, was treated with subcutaneous insulin 68 units twice daily initially, rising rapidly to 68 units four times a day. The oedema improved with diuretic therapy.

The patient was discharged home requiring 272 units of insulin daily to control his diabetes. He was readmitted the following day as an emergency complaining of severe frontal headaches and vomiting. He had marked photophobia and the history obtained from relatives suggested that he had also fainted. The fundi were normal. He recovered rapidly over 48 hours. A CT scan of the brain revealed a large sella turcica and several cerebral metastases. His symptoms were initially attributed to metastases and, despite hypercortisolaemia, he was treated with a high dose of oral dexamethasone (2 mg q.d.s.). Irradiation to the whole brain was given over 10 days to a total dose of 300 c GY.

Although a single dose of the somatostatin analogue SMS 201-995 (Sandoz UK) 50 µg subcutaneously had no acute effect on circulating levels of glucose, insulin, C-peptide, ACTH or cortisol, treatment was commenced at a subcutaneous dose of 50 µg b.d. on 30 August 1984. This produced no significant change in the clinical condition, plasma growth hormone, cortisol, blood glucose levels, or insulin requirements.

After 10 days acute copious diarrhoea developed. Insulin requirements fell dramatically and treatment with SMS 201-995 was stopped after which the diarrhoea gradually settled. Biochemical evidence now showed that the patient had suffered pituitary infarction, most likely during his previous acute admission. The episode of diarrhoea is unexplained but may have been due to the SMS 201-995.

Table I Selected results obtained prior to treatment and pituitary infarction

Random blood glucose	29.4 mmol/l
Plasma albumin	32 g/l
Random plasma GH	44 mU/l
Plasma IGF-I (insulin like growth factor I)	4.16 U/l normal range 0.4–2)
Random plasma cortisol	1016 nmol/l
Random plasma C-peptide	6.7 µg/l
Insulin antibodies	none detected
Plasma total thyroxine	101 nmol/l
Plasma testosterone	6 nmol/l
Urinary free cortisol	grossly elevated
Urinary VMA excretion (vanillylmandelic acid)	normal
Urinary 5HIAA excretion 5 hydroxy indole acetic acid)	normal
Plasma ACTH	300 µg/l (normal range 20–80)
Plasma GHRH	45,000 ng/l (normal range 10–60)

Table II TRH/LHRH stimulation test

	Plasma						
	LH IU/l	FSH IU/l	TSH mU/l	T4 nmol/l	GH mU/l	Cortisol nmol/l	Prolactin mU/l
Basal	1	1	2.2	87.0	6.2	2058	2511
100 µg LHRH and 200 µg TRH intravenously							
20 min	–	–	14.3	–	27.1	–	1538
30 min	50	9	–	–	–	–	1014
60 min	27	4	10	–	11.2	–	473

Pituitary function tests were performed on 1 October 1984. Basal TSH, LH, follicle stimulating hormone (FSH) and growth hormone were below the level of detection and showed no response to TRH and LHRH. Both total thyroxine (34 nmol/l) and 'free' thyroxine (4.0 pmol/l) were low but plasma cortisol, ACTH and GHRH levels remained high. Over the 6 months period following the presumed pituitary infarction, plasma insulin-like growth factor I (IGF-1) levels fell from 5.6 to 0.2 IU/l and prolactin levels fell to less than 50 mU/l.

Pre-infarction plasma levels of gastrin, vasoactive intestinal polypeptide (VIP), glucagon, calcitonin, somatostatin and bombesin were normal at all times. Corticotrophin releasing factor (CRF) was undetectable in plasma both before and after pituitary infarction.

Immunoperoxidase staining of the tumour biopsy showed both ACTH and GHRH. No immunochemical CRF, GH or 5 hydroxytryptamine (5HT) was demonstrated. After further courses of chemotherapy and radiotherapy the patient gradually deteriorated and died some 9 months after the events described. A post-mortem examination was not obtained.

Discussion

This patient demonstrates ectopic production of both GHRH and ACTH by an adenoid cystic carcinoma. These tumours arise in the bronchus, trachea, breast or salivary gland and have a characteristic histological appearance.⁶ They have not previously been known to be associated with ectopic GHRH or ACTH production.

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Although arterio-venous differences across the tumour were not measured the evidence for ectopic production is good: (i) the failure of plasma ACTH and cortisol levels to respond to high dose dexamethasone;⁷ (ii) the persistence, following pituitary infarction of high plasma cortisol and ACTH levels; and (iii) the immunocytochemical demonstration of ACTH in the tumour.

Similarly, the presence of grossly elevated levels of GHRH in peripheral venous blood, with a fall in the high levels of growth hormone and IGF-1 but not GHRH, following pituitary infarction, together with the large amounts of GHRH demonstrated immunocytochemically in the tumour tissue, point to ectopic secretion of GHRH.

The somatostatin analogue, SMS 201-995, failed to suppress the elevated levels of GH, insulin, glucose, GHRH or ACTH which contrasts with the findings in regular acromegaly where somatostatin and its analogues consistently lower basal GH^{8–12} and insulin levels¹³ and block the response to exogenous GHRH.^{8–12}

The acute onset diarrhoea may have been a side effect of the drug but the case was complicated by pituitary infarction. Pancreatic steatorrhoea has been reported¹⁷ in patients receiving long term therapy with a higher dose of SMS 201-995.

The findings of a rise in plasma GH in response to TRH is in accord with the findings of Schulte¹⁴ in another patient with a GHRH-producing tumour. Our patient also had insulin-dependent diabetes mellitus – itself a cause of GH responsiveness to TRH.¹⁵ The reason for the GH response to TRH is not clear; it has been suggested that somatotroph hyperplasia secondary to hyperstimulation by GHRH permits TRH to become a secretagogue for GH¹⁶ but this must still be considered conjectural.

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