Pergamon

European Journal of Cancer Vol. 31A, No. 12, pp. 2109–2112, 1995

0959-8049/95 $9.50+0.00

0959-8049(95)00388-6

Short Communication

Colonic Adenocarcinoma Associated Ectopic ACTH Secretion: A Case History

D.A. Anthoney,[1] D.J. Dunlop,[1] J.M. Connell[2] and S. B. Kaye[1]

[1]Beatson Oncology Centre; and [2]Department of Medicine and Therapeutics, Western Infirmary, Dumbarton Road, Glasgow G12 8QQ, U.K.

A 57-year-old woman developed features of Cushing's syndrome after resection of a Duke's C adenocarcinoma of the sigmoid colon. Biochemical and endocrine investigation indicated ectopic production of adrenocorticotrophic hormone (ACTH) as the cause for her condition. Hepatic metastases were detected by computed tomography (CT) scan. Histology of the original tumour displayed neuroendocrine characteristics but no definite evidence of ACTH synthesis. Treatment was instituted to control her hypercortisolism, and chemotherapy initiated to reduce the production of ectopic hormone. A clinical, biochemical and radiological response was obtained with complete resolution of her Cushing's syndrome. The tumour relapsed after several months with distant metastases, but no further endocrine abnormality was noted. A review of ectopic ACTH producing adenocarcinoma is given along with a discussion of the major pathological and therapeutic features of the case.

Key words: adenocarcinoma, Cushing's syndrome, ectopic ACTH
Eur J Cancer, Vol. 31A, No. 12, pp. 2109–2112, 1995

INTRODUCTION

SINCE ITS first description by Brown [1] in 1928, the ectopic production of adrenocorticotrophic hormone (ACTH) by non-endocrine tumours has become a well recognised paraneoplastic syndrome. Oat-cell carcinoma of the bronchus is the most commonly identified source of eptopic ACTH, with malignant thymic tumours, carcinoid tumours, phaeochromocytoma and islet cell tumours of the pancreas constituting the majority of the rest [2]. All these tumours are thought to have neuroendocrine characteristics. Synthesis of ACTH by other tumour types, for example adenocarcinoma, is very rare, being reported as isolated case reports [3–9]. One case of colonic adenocarcinoma associated ectopic ACTH syndrome has been reported previously [10]. In that case, the patient presented with features of, but not classical, Cushing's syndrome. An adrenalectomy was attempted to control the excess glucocorticoid production; however, no other form of treatment was possible in view of the rapid progression of the disease. The patient died within 4 months of the onset of symptoms and, at autopsy, bioassay of the colonic tumour revealed increased ACTH activity.

Non-endocrine tumour cells may produce ACTH more commonly than is normally recognised. In some cases, especially of small cell bronchial carcinoma, this may be because the tumour progresses so quickly that clinical features resulting from the ectopic hormone do not have time to develop. In other cases with signs and symptoms of hypercortisolism, the detection of a neoplastic source may prove very difficult. Multiple investigations involving computed tomograhpy (CT), magnetic resonance imaging (MRI) and venous sampling techniques may be required in an attempt to identify the tumour. This report presents a case of metastatic rectal adenocarcinoma with clinical features of Cushing's syndrome and an elevated plasma ACTH level.

CASE HISTORY

A 57-year-old woman presented to a Glasgow hospital with a 4 month history of painful and swollen joints, hepatomegaly, mild jaundice and rectal bleeding. A diagnosis of systemic lupus erythematosis was made by the detection of an anti-Sm antibody (SMA) and a positive antinuclear factor (1 in 1000 units homogeneous). Drug-induced hepatitis, due to a non-steroidal anti-inflammatory preparation, was considered to be responsible for her abnormal liver function as this improved on stopping the medication. Sigmoidoscopy detected an irregular lesion at 15 cm from the anal margin, biopsy of which revealed an invasive, moderately differentiated adenocarcinoma. It was staged as a Duke's C carcinoma at subsequent resection, and abdominal

Correspondence to D.A. Anthoney at the C.R.C. Department of Medical Oncology, University of Glasgow, Alexander Stone Building, Garscube Estate, Bearsden, Glasgow G61 1BD, U.K.
Received 16 Jan. 1995; accepted 15 Mar. 1995.

ultasonography and CT revealed no abnormality of the liver parenchyma at that time. She made a relatively uneventful immediate postoperative recovery and was discharged.

One month later she was re-admitted with facial swelling, proximal weakness of her legs and a marked hypokalaemic alkalosis. Despite the administration of intravenous potassium supplements, the hypokalaemia persisted and was associated with progression of the proximal weakness and peripheral oedema. A clinical diagnosis of Cushing's syndrome was made and confirmed by the results of endocrine analysis (Table 1); metyrapone (250 mg twice a day) was started in an attempt to control the excess cortisol secretion. Subsequent investigations revealed a high plasma ACTH with an elevated serum cortisol and the failure of the cortisol to fall following high dose dexamethasone (2 mg orally four times a day) for 4 days. This confirmed the diagnosis of ectopic ACTH production. An abdominal CT scan revealed multiple liver metastases and also showed general enlargement of both adrenal glands consistent with hyperstimulation (Figure 1a.) She was, therefore, referred to the Beatson Oncology Centre, Glasgow, U.K. for her further management.

At the time of referral to the Beatson Oncology Centre, Glasgow, U.K. the clinical features of her hypercortisolism included a marked proximal myopathy, centripetal obesity with associated "moon" face, and fragility of the skin with multiple bruises. Clinical examination revealed hepatomegaly and marked proximal muscle wasting of the lower limbs. Serum biochemistry showed elevation of hepatic transaminases, alkaline phosphatase and γGT as well as hypokalaemic alkalosis. Her metyrapone therapy was unchanged and she was taking slow release oral potassium supplements. To improve the control of the hypercortisolism, the dose of metyrapone was increased and aminoglutethamide was added at an initial dose of 250 mg twice daily. The doses of these drugs were increased in an attempt to suppress adrenal corticosteroid synthesis as indicated by measurement of serum and urinary cortisol. Spironolactone was also used to help control the hypokalaemia.

A review of the histology of the original rectal tumour, specifically looking for evidence of ACTH production, indicated that, although there was evidence of neuroendocrine differentiation, there was no staining for ACTH nor detection of the mRNA of its precursor, pro-opiomelanocorticotrophin (POMC). Despite these negative findings, it was considered unlikely that there was an additional primary tumour as the source of the ectopic hormone, and there was no radiographic evidence for one. A regimen of chemotherapy active against both a metastatic adenocarcinoma of the colon and a neuroendocrine type of tumour was, therefore, instituted. This consisted of intravenous carboplatin given on day 1 and folinic acid/5-fluorouracil (5-FU) given on days 1, 2, 14 and 15 of a 28 day cycle. The dose of carboplatin was calculated using the patient's measured creatinine clearance and an AUC of 5. The folinic acid was given at a dose of 200 mg/m^2 and the 5-FU administered as a bolus of 500 mg/m^2 followed by a 22 hr infusion of 500 mg/m^2. Her urinary free cortisol, serum cortisol and dehydroepiandrosterone sulphate (DHES) were used as markers of the response to the steroid enzyme inhibition while the ACTH was used as a tumour marker. Figure 2 shows the response of these parameters to her treatment.

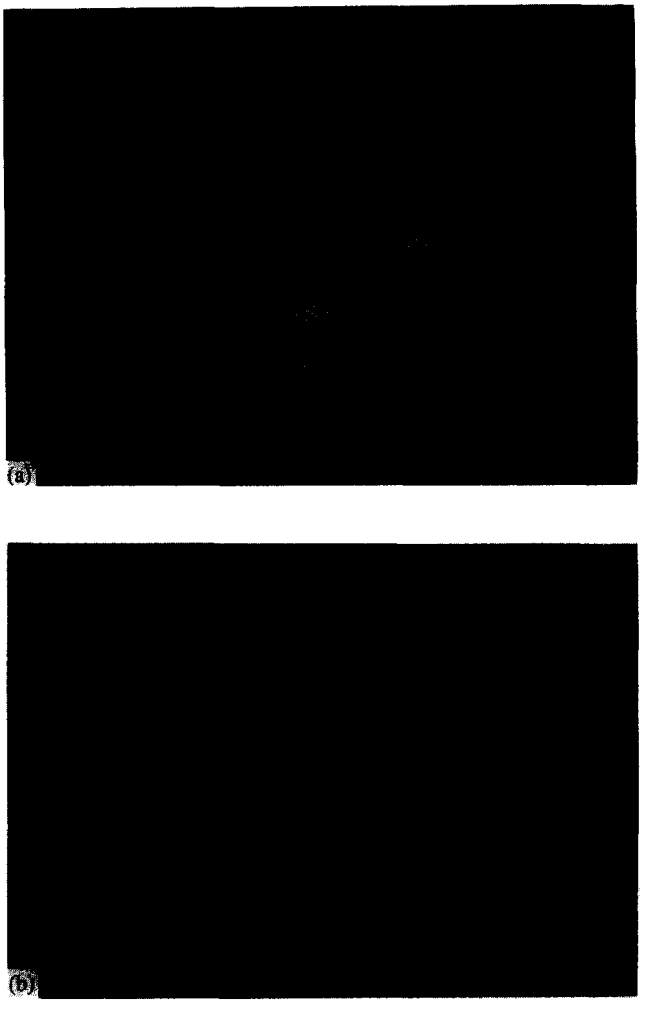

Figure 1. (a) Enhanced CT scan of upper abdomen showing several large metastases within the liver. (b) Enhanced CT scan of upper abdomen after completion of chemotherapy showing resolution of metastatic lesions.

*Table 1. Biochemical features suggesting a diagnosis of Cushing's syndrome during the initial investigation, with those indicative of an underlying ectopic ACTH secretion marked with **

Serum potassium	1.9–2.4 mmol/l*	(3.3–4.7 mmol/l)
Serum bicarbonate	20–24 mmol/l*	(22–30 mmol/l)
Serum cortisol (8 am)	1125–1536 nmol/l	(150–700 nmol/l)
Urinary free cortisol:creatinine ratio	1000 mmol/mol creatinine	(2–25 mmol/mol creatinine)
Plasma ACTH	80–105 mU/l*	(<20 mU/l)
Serum cortisol (8 am) after low dose dexamethasone for 48 h	1074 nmol/l	(150–700 nmol/l)
Serum cortisol (8 am) after high dose dexamethasone for 48 h	1332 nmol/l*	(150–700 nmol/l)

Normal range of values in parentheses.

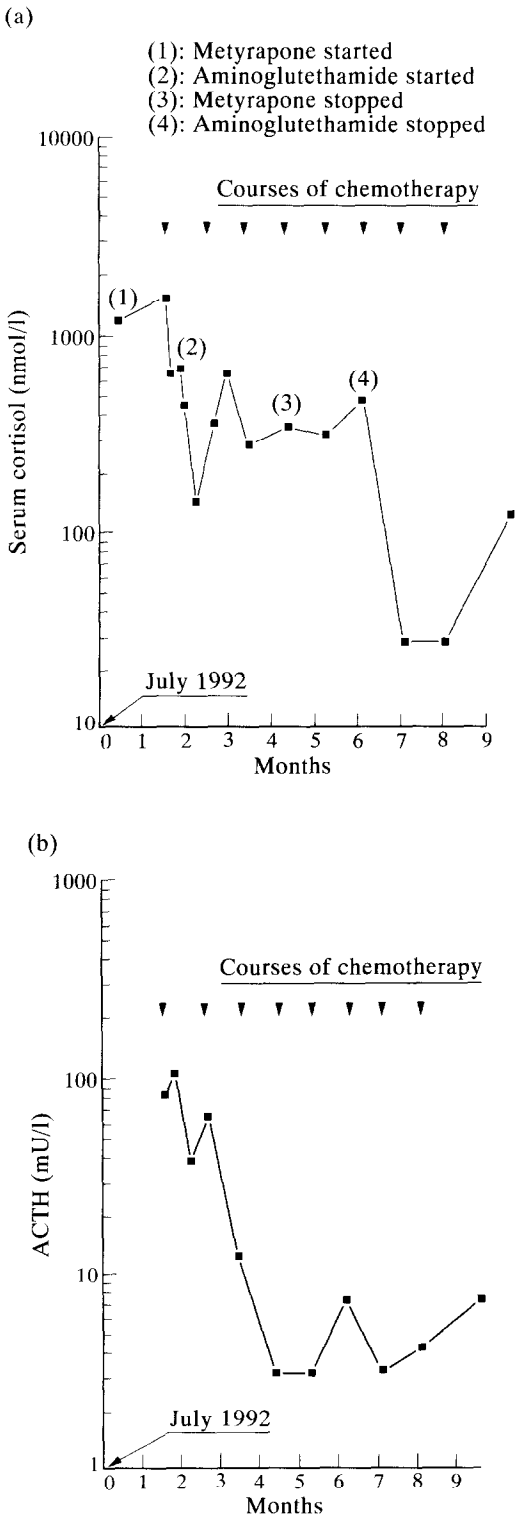

Figure 2. (a) Fall in random serum cortisol during treatment with chemotherapy. (b) Fall in plasma ACTH during treatment with chemotherapy.

She received eight courses of this chemotherapy regimen over the next 7 months. Treatment was delayed on one occasion owing to the development of thrombocytopenia, and subsequently 5-FU/folinic acid was given monthly with, in addition, a reduction in the dose of 5-FU to 400 mg/m^2. Over the course of her treatment, she showed a good clinical response with a reduction in her serum cortisol and urinary free cortisol levels. In view of this, the doses of metyrapone and aminoglutethamide were reduced and both drugs were eventually stopped. The fall in serum ACTH indicated a response to chemotherapy, and this was confirmed radiologically by repeat CT scanning of the liver which showed resolution of the metastatic lesions (Figure 1b.) A major symptomatic improvement was also observed over the course of her treatment, and the patient returned to work on a part-time basis after its completion. The complete remission persisted for several months before she developed subcutaneous metastases, although with no evidence of a return of Cushing's syndrome or of other metastases. Radiotherapy was applied to these lesions on three occasions (35 Gy in 10 fractions on two occasions and 45 Gy in 10 fractions on the last) with their complete resolution. In September 1993, she presented with a large right sided tonsilar lesion. Excision of the affected tonsil and subsequent histology showed it to be extensively infiltrated with an undifferentiated carcinoma of large cell type with no evidence of intracytoplasmic mucin. It was shown that there were similarities between the tonsilar lesion and areas of undifferentiated tumour in the original adenocarcinoma suggesting that this was a metastatic lesion from the rectal primary. Radiotherapy was planned for the tonsillar bed, but before this could be given she developed signs suggestive of raised intracranial pressure and an enhanced CT scan detected a mass in the right cerebellar hemisphere with compression of the fourth ventricle. She started dexamethasone treatment to reduce the associated cerebral oedema and cranial irradiation was instituted (20 Gy in five fractions). Despite this treatment, her disease continued to progress and she died in December 1993.

DISCUSSION

This report presents a case of metastatic rectal adenocarcinoma with clinical features of Cushing's syndrome and an elevated plasma ACTH level. The signs of hypercortisolism only became manifest upon the development of hepatic metastases after resection of the primary tumour. The diagnosis was based on the high levels of plasma ACTH and the lack of suppression of serum cortisol levels and urinary cortisol metabolites upon administration of high dose dexamethasone. Surprisingly, immunohistochemistry of the resected tumour failed to detect production of ACTH or its precursor molecule, POMC, within cells. It did, however, identify Chromogranin A, a matrix protein present in the storage granules of neuroendocrine cells and, therefore, consistent with possible neuroendocrine activity. Chromogranin A may also be associated with an increased sensitivity to chemotherapy when present in certain tumours [11]. Despite the inability to identify ACTH synthesis within the primary tumour, it was still felt that the metastatic adenocarcinoma was the source of the endocrine disturbance. Extensive radiological examination with X-rays and CT had failed to detect other lesions which could have been responsible for the clinical picture. Additionally, upon resolution of the hepatic metastases with treatment, the levels of ACTH returned to normal, suggesting cessation of ectopic production. There are several possible explanations for the failure to detect ACTH in the primary tumour cells. It may be that the form of hormone produced by the tumour cells was not detected by the antibody used for detection. However, Northern blot analysis of the tumour revealed no evidence of mRNA for POMC. A more interesting possibility is that the tumour was secreting another hormone which acted upon the pituitary gland to stimulate release of ACTH. This has been reported before for both corticotrophin releasing factor [12] and a bombesin-like peptide [13].

Despite the malignant nature of the majority of tumours expressing ectopic ACTH, very few cases have been reported in which the tumour itself, as opposed to the symptoms due to the excess cortisol, has been treated. Several cases of adenocarcinoma of the lung with associated ACTH production have been cured by surgical resection [14]. This case is unique in that a complete radiological and clinical remission of the metastatic adenocarcinoma along with resolution of the ectopic ACTH synthesis was obtained by combination chemotherapy, although ultimately lasting for only several months. 5-FU is standard therapy for metastatic adenocarcinoma of the colon and as such was an appropriate first-line treatment in this case. However as the primary lesion had shown evidence of neuroendocrine differentiation, carboplatin was also added as a second antineoplastic agent. Carboplatin demonstrates a good response rate in small cell carcinoma of the lung [14]. Gratifyingly, the tumuor responded to this combination with both radiological and biochemical evidence of complete remission. It is not possible to assume the combination of agents had a better effect than either of the drugs would have had alone. Interestingly, when the tumour eventually relapsed, initially with the cutaneous metastases and then with tonsillar and cerebral lesions, there was no biochemical or clinical evidence of ectopic ACTH prodcution. Histological analysis of the tonsillar metastasis showed it to consist of less well differentiated tissue than the primary tumour. For a tumour to express hormones such as ACTH, a certain degree of differentiation may be required. Once this is lost, with progression of the tumour, synthesis may stop.

Although she eventually succumbed to her disease, this patient had a reasonable quality of life during and after treatment. Tackling the source of ectopic hormone production as well as inhibiting its effects may well be of greater benefit in these rare cases.

1 Brown WH. A case of pleuriglandular syndrome: "Diabetes of bearded women". *Lancet* 1928, **2**, 1022–1023.

2. Imura H, Matsukura S, Yamamoto H, *et al.* Studies on ectopic ACTH producing tumours. 2. Clinical and biochemical features of 30 cases. *Cancer* 1975, **35**, 1430–1437.

3. Myers AE, Hardman JM, Worsham GF, *et al.* Adenocarcinoma of the lung causing ectopic adrenocorticotropic hormone syndrome. *Arch Intern Med* 1982, **142**, 1387–1389.

4. Sachs BA, Becker N, Bloomberg AE, *et al.* Cure of ectopic ACTH syndrome secondary to adenocarcinoma of the lung. *J Clin Endocrin* 1970, **30**, 590–597.

5. Fujiwara Y, Mori H, Suminoto M, *et al.* Ectopic ACTH-producing adenocarcinoma of the stomach. *Hepato-Gastroenterology* 1982, **39**, 481–483.

6. Spence RW, Burns-Cox CJ. ACTH secreting "apudoma" of gallbladder. *Gut* 1975, **16**, 473–476.

7. Newmark SR, Dluhy RG, Bennett AH. Ectopic adrenocorticotropin syndrome with prostatic carcinoma. *Urology* 1975, **5**, 817–820.

8. Marks AD, Kim YN, Kroop HS. Ectopic production of ACTH by a minor salivary gland tumour. *Ann Intern Med* 1975, **83**, 521–522.

9. Sterling RK. Ectopic ACTH syndrome associated with anorectal carcinoma. Report of a case and review of the literature. *Digest Dis Sci* 1993, **38**, 955–959.

10. Balsam A, Bernstein G, Goldman J, *et al.* Ectopic adrenocorticotropin syndrome associated with carcinoma of the colon. *Gastroenterology* 1972, **62**, 636–641.

11. Park J, Choe GY, Helman J, *et al.* Chromogranin-A expression in gastric and colon cancer tissues. *Int J Cancer* 1992, **51**, 189–194.

12. Carey RM, Verma SK, Drake CR, *et al.* Ectopic secretion of corticotropin-releasing factor as a cause of Cushing's syndrome. *N Engl J Med* 1984, **311**, 13–20.

13. Howlett TA, Price J, Hale AC, *et al.* Pituitaty ACTH dependent Cushing's syndrome due to ectopic production of a bombesin-like peptide by a medullary carcinoma of the thyroid. *Clin Endocrinol* 1985, **22**, 91–101.

14. Bunn PA. Clinical experiences with carboplatin (paraplatin) in lung cancer. *Semin Oncol* 1992, **19**, suppl. 2, 1–11.