MedCrave
Step into the World of Research

Journal of Cancer Prevention & Current Research

Ectopic ACTH Production: Diagnosis, Treatment and Prognosis

Abstract

Cushing's syndrome due to ectopic ACTH as a result of metastatic malignancy invariably has a poor prognosis. In addition to tumour growth, diabetic and infective complications are causes of death. A multidisciplinary approach is needed with the focus of care being on management of endocrine abnormalities, control of symptoms and optimising quality of life. The adverse prognosis associated with these cancers should be taken into account when deciding on whether or not to pursue active oncological treatment with chemotherapy. In this case report, a 69-year-old patient presented with symptoms and signs of Cushing's syndrome, which on further investigation was shown to be due to an ectopic ACTH-secreting metastatic small cell cancer of unknown primary. Treatment with palliative carboplatin etoposide chemotherapy and metyrapone was started, but unfortunately after one cycle of chemotherapy the patient died following hospital admission with poor diabetic control and non-neutropenic sepsis. We discuss the key issues in the diagnosis and management of this condition.

Case Report

Volume 6 Issue 3 - 2016

Tom Wells[1]*, Andrew Day[2] and Serena Hilman[3]

[1]*Consultant Medical Oncologist, Weston General Hospital, UK*
[2]*Consultant in Chemical Pathology, Weston General Hospital, UK*
[3]*Consultant Clinical Oncologist, Weston General Hospital, UK*

***Corresponding author:** Tom Wells, Consultant Medical Oncologist, Weston General Hospital, Weston-super-Mare, UK, Email: thomas.wells@nhs.net

Received: October 26, 2016 | **Published:** December 14, 2016

Case Report

A 69-year-old woman presented with a four-week history of facial and bilateral leg swelling. She also described symptoms of proximal myopathy. Her past medical history included osteoporosis and osteoarthritis. Routine medication was a weekly bisphosphonate, aspirin and St John's Wort. Clinical examination identified bilateral pitting oedema to the knees and Cushingoid facies. Her blood pressure was 150/70 mm Hg. Investigations performed is listed in Table 1.

These investigations showed:

A. hypokalaemic alkalosis and an inappropriately high urine potassium indicating a renal route of potassium loss;

B. Cushing's syndrome due to ectopic ACTH as a result of metastatic malignancy, with liver metastases (Figure 1), normal adrenal glands and no obvious primary evident on CT chest abdomen and pelvis;

C. Normal pituitary gland and no intra-cranial metastases on MRI brain.

The non-specific increases in the serum concentrations of tumour markers (CA125, CA15-3, CA19-9) were of no diagnostic value. The patient underwent a liver biopsy which revealed small cell carcinoma.

Palliative carboplatin etoposide chemotherapy was subsequently commenced to treat the cancer and metyrapone was given to treat the endocrine abnormality. After one cycle of chemotherapy she developed diabetes and was admitted to hospital with poor diabetic control and non-neutropenic pneumonia. Unfortunately, she deteriorated rapidly and passed away only four months after the development of her symptoms.

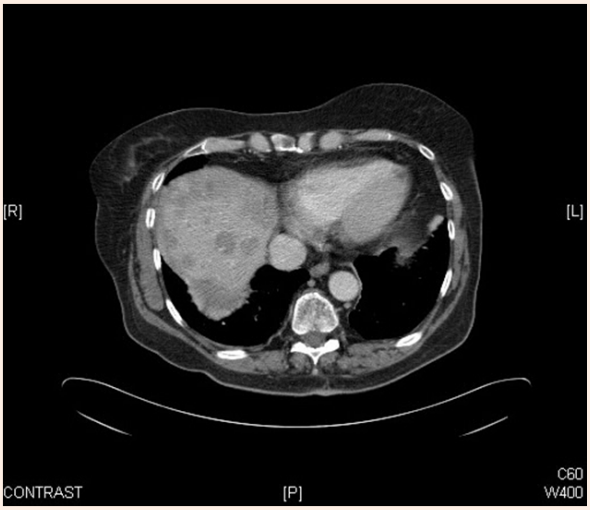

Figure 1: Computerised tomography scan of chest, abdomen and pelvis: extensive liver metastases.

Discussion

Cushing's syndrome as a result of ectopic ACTH production has been reported in association with a variety of malignant tumours. Most commonly it is seen with neuroendocrine tumours such as small cell lung cancer (accounting for about 50% of cases of ectopic ACTH syndrome [1,2]), carcinoid syndrome [3] and medullary carcinoma of the thyroid [4]. It has also been seen in cases of adenocarcinoma of the lung [5], breast [6], prostate [7] and pancreas [8]. Ectopic ACTH syndrome is evident in approximately 2 to 5% of patients with small cell lung cancer

[9-11] and it occurs in both limited and extensive stage disease. Ectopic ACTH syndrome invariably has a poor prognosis unless it is associated with carcinoid syndrome.

Patients are diagnosed with ectopic ACTH syndrome if they have clinical signs and symptoms of excess corticosteroid production and at least two of the following criteria: spontaneous hypokalemia (potassium < 3.2 mmol/l), plasma cortisol level > 660 nmol/l with loss of diurnal variation and / or lack of suppressibility by dexamethasone, plasma ACTH level > 22 pmol/l, and 24-hour urinary free cortisol level > 400 nmol/day [9]. In addition to these tests, inferior petrosal sinus sampling of ACTH levels is an invasive technique which is sometimes used to differentiate between ectopic ACTH syndrome and Cushing's disease (Cushing's syndrome due to pituitary adenoma) [12]. See Table 2 for a summary of the investigations used to determine the different causes of Cushing's syndrome.

Table 1: Investigations performed.

Serum potassium	2.2 mmol/l (low) [normal range 3.5 – 5.1]
Serum bicarbonate	37.2 mmol/l (high) [normal range 22 – 29]
Urine potassium concentration	46 mmol/l (high)
Renal function	Normal
Random serum cortisol concentration	1303 nmol/l (high)
Urinary cortisol excretion	2444 nmol/l/24 hrs (high) [normal range < 120]
Plasma ACTH concentration	175ng/l (high) [normal range < 46]
Plasma renin activity	0.3 pmol/ml/h (low) [normal range 2.8 – 4.5]
Aldosterone	< 75 pmol/l (low) [normal range 100 – 800]
Aldosterone/renin ratio	< 250 [< 800 excludes Conn's syndrome]
Low dose dexamethasone suppression test	Cortisol not suppressed
High dose dexamethasone suppression test	Cortisol not suppressed
Corticotrophin releasing hormone stimulation test	ACTH and cortisol not increased
MRI brain	No abnormality
CT chest abdomen pelvis	Extensive liver metastases, normal adrenal glands and no obvious primary (Fig 3)
Serum CA125	66 U/L [normal range < 35]
Serum CA15-3	158 kU/L [normal range < 25]
Serum CA19-9	240 kU/L [normal range < 27]

Table 2: Investigations to determine different causes of Cushing's syndrome.

	Cushing's Disease (Pituitary Adenoma)	Primary Adrenal Cushing's syndrome	Ectopic ACTH Syndrome	Iatrogenic Cushing's Syndrome
Plasma Cortisol	High	High	High	High
24 hour urinary free Cortisol	High	High	High	High
Plasma ACTH	High	Undetectable or low	Normal to high	Low
Low dose dexamethasone suppression test	Cortisol not suppressed	Cortisol not suppressed	Cortisol not suppressed	Cortisol not suppressed
High dose dexamethasone suppression test	Cortisol suppressed	Cortisol not suppressed	Cortisol not suppressed	Cortisol not suppressed
Corticotrophin releasing hormone stimulation test	ACTH and Cortisol increases	ACTH and Cortisol does not increase	ACTH and Cortisol does not increase	ACTH and Cortisol does not increase
MRI brain	Pituitary adenoma detected in 70% of cases	No abnormality	No abnormality	No abnormality
CT chest abdomen pelvis	No abnormality	Adrenal adenoma or adrenal hyperplasia	Malignant disease identified	No abnormality
Inferior petrosal sinus (IPS) sampling[12]	IPS:plasma ACTH ratio > 2 (> 3 if corticotrophin releasing hormone given) indicates a pituitary source of ACTH[12]	Not indicated	IPS:plasma ACTH ratio ≤ 2 (≤ 3 if corticotrophin releasing hormone given) suggests ectopic source of ACTH[12]	Not indicated

It should be noted that clinical signs of Cushing's syndrome are not always evident in ectopic ACTH syndrome, with only metabolic abnormalities present in some patients. Ectopic ACTH may therefore mimic Conn's syndrome (primary hyperaldosteronism), except that plasma aldosterone and renin concentrations are low. This reflects the rapid onset of severe hypercortisolism to a level where there is significant cross-reactivity at the mineralocorticoid (aldosterone) receptor in the kidney.

Patients with ectopic ACTH syndrome have a high incidence of infection, diabetes and hypertension resulting from steroid excess. Death is invariably due to tumour growth, but infection (neutropenic and non-neutropenic) has often been noted to be the cause of death. Studies suggest that ectopic ACTH production is an adverse prognostic factor, although the reason for this is unclear. Possibilities are an increased risk of infection and diabetic complications and perhaps that ACTH excess signifies a more aggressive cancer.

Treatment strategies include treatment of the underlying cancer, treatment of the endocrine abnormality and treatment of complications (infection, diabetes and hypertension). In one case series of 14 patients with small cell lung cancer and ectopic ACTH syndrome (five with limited stage disease, nine with extensive stage disease) [9], objective tumour responses to chemotherapy were seen in three patients (complete response in two, partial response in one). Median survival was 10 and 5 months in patients with limited and extensive stage disease, respectively, with median survival for the entire group of 14 patients being 5½ months. In another study of 10 patients with small cell lung cancer and assessable for hormone response to chemotherapy [10], there was a complete, partial and no hormone response seen in two, five and three patients. Median survival was only 3.57 months illustrating the poor outlook of this condition. While chemotherapy has been shown to improve median survival in patients with metastatic small cell cancer [13], there is no evidence that it improves survival for patients with small cell cancer and ectopic ACTH production.

There have been case reports which agree with this poor prognosis. One was of a 69-year-old patient with ACTH-secreting neuroendocrine carcinoma of the Ampulla of Vater and liver metastases, in which the patient died after four months despite administration of irinotecan cisplatin combined chemotherapy [14]. Another was of a 48-year-old patient with sigmoid colon

neuroendocrine carcinoma and liver metastases, in which the patient died of neutropenic sepsis after two cycles of palliative chemotherapy [15]. The fact that survival is so poor in these patients makes one have to question whether chemotherapy has any significant impact on survival at all. However, there have been some case reports in which patients do better. One was of a 55-year-old woman who had total thyroidectomy 20 years previously and then developed ectopic ACTH as a result of recurrence with metastatic disease affecting lungs, bones and the mediastinal and neck nodes [4]. Treatment with the kinase inhibitor vandetanib resulted in a radiological, biochemical and clinical improvement within two months of treatment. Another case report was of a 27-year-old woman with ACTH-secreting poorly differentiated pancreatic neuroendocrine carcinoma with ovarian and pelvic metastases, which was treated with extensive surgery (partial pancreatectomy, splenectomy, bilateral oophorectomy and excision of peritoneal nodules) followed by chemotherapy [16]. Subsequent pelvic nodal recurrence happened 19 months after surgery and this didn't respond to second line chemotherapy.

Other treatments to improve symptoms due to ectopic ACTH production include medications to decrease endogenous steroid production by the adrenal glands, such as metyrapone [17-18], ketoconazole [19], aminoglutethimide [17] and somatosatin analogues [20,21]. Adrenal ablation (by mitotane, embolisation or adrenalectomy) is another treatment option for decreasing endogenous steroid production. Diabetic and blood pressure control is important and requires careful monitoring.

Metyrapone inhibits adrenal steroid synthesis by inhibiting the enzyme steroid 11β-hydroxylase and subsequently this decreases the conversion of 11-deoxycortisol to the more potent glucocorticoid cortisol. It has been shown to produce clinical, hormonal and biochemical improvement in patients with ectopic ACTH syndrome. In one case series [18], metyrapone given at a median dose of 4000 mg/day (range 1000 - 6000 mg/day) resulted in a reduction in cortisol levels in 13 of 18 (70%) patients with ectopic ACTH syndrome. Cortisol levels decreased from a median level of 1023 nmol/l (range 823 - 6354 nmol/l) to < 400 nmol/l. The medication was well tolerated with the most common side effects being transient hypoadrenalism and hirsuitism.

Somatostatin analogues have also shown promise in achieving hormonal improvements in carcinoid tumours. In one study, two patients with ACTH syndrome due to lung carcinoid tumours were treated with the long acting somatostatin analogue SMS 201-995 (Sandostatin) [21]. One patient had a 50% reduction in serum ACTH, achieved within 4 hours of a single 50 mcg dose. In the other patient a clinical and biochemical remission was maintained for 10 weeks on 100 mcg three times daily.

In another study [19], ketoconazole has been shown to achieve clinical, hormonal and biochemical responses. Fifteen patients with ectopic ACTH syndrome were assessable for response to ketoconazole given in a daily dose ranging from 400 to 1200 mg. After starting ketoconazole, hypokalemia improved in 13 of 14 assessable patients, although only five were able to discontinue potassium supplementation and potassium-conserving medications. Metabolic alkalosis completely responded in 8 of 11 assessable patients. Seven of 10 assessable patients with new or worsened diabetes had improved glycemic control, and in one of the patients insulin or oral hypoglycaemic drugs could be stopped. All eight assessable patients with new or worsened hypertension had improved blood pressure control, although antihypertensives could be discontinued in only one patient. Hormonal response was assessed using urinary free cortisol levels in 12 patients, with a complete response (normalisation of urinary free cortisol level) seen in five patients and a partial response in three patients. It should be noted that patients received concurrent chemotherapy, therefore making it difficult to determine whether chemotherapy or ketoconazole had achieved the response. Of importance is that in those who have a hormone response on ketoconazole, there is an inadequate steroid response to stress (e.g., infection). This has led to the recommendation that maintenance corticosteroids should be given to those who have normalisation of hormones and that early steroid replacement be given at times of stress in those who have a partial hormone response [19,22,23]. This should also be the practice in those treated with other medications used to decrease endogenous steroid production, such as metyrapone and aminoglutethimide.

In summary, treatment of ectopic ACTH syndrome due to malignancy based on current evidence would be: urgent referral to oncology for assessment and for consideration of starting active oncological treatment; consideration of therapies to reduce endogenous steroid production; give steroid replacement in complete hormone responders and at times of physiological stress in partial hormone responders; early treatment of suspected infection; active management of glucose intolerance and hypertension. This is a multidisciplinary problem and needs involvement of endocrinology, oncology, clinical biochemistry, histopathology, radiology, and palliative care specialties. Although ideally randomised controlled trials should assess the interventions involved, they are unlikely to be feasible, given the rarity of the condition and that data to date are based on case series. Instead future evidence is likely to be gained from adopting a national framework of recommendations for practice and auditing outcomes accordingly.

References

1 White A, Clark AJL, Stewart MF (1990) The synthesis of ACTH and related peptides by tumours. Baillieres Clin Endocrinol Metab 4(1): 1-26.

2 Müller OA, von Werder K (1992) Ectopic production of ACTH and corticotropin-releasing hormone (CRH). J Steroid Biochem Mol Biol 43(5): 403-408.

3 Torpy DJ, Mullen N, Ilias I, Nieman LK (2002) Association of hypertension and hypokalemia with Cushing's syndrome caused by ectopic ACTH secretion: a series of 58 cases. Ann N Y Acad Sci 970: 134-144.

4 Bseiso H, Lev-Cohain N, Gross DJ, Grozinsky-Glasberg S (2016) Vandetanib induces a marked anti-tumor effect and amelioration of ectopic Cushing's syndrome in a medullary thyroid carcinoma patient. Endocrinol Diabetes Metab Case Rep 2016 pii:16-0082.

5 Myers EA, Hardman JM, Worsham GF, Eil C (1982) Adenocarcinoma of the lung causing ectopic adrenocorticotropic hormone syndrome. Arch Intern Med 142(7): 1387-1389.

6 Parker MS, Jackson R (1984) Ectopic ACTH syndrome associated with breast carcinoma. South Med J 77(4): 518-521.

7 Ghali VS, Garcia RL (1984) Prostatic adenocarcinoma with carcinoidal features producing adrenocorticotropic syndrome. Immunohistochemical study and review of the literature. Cancer 54: 1043-1048.

8 Gullo L, De Giorgio R, D'Errico A, Grigioni W, Parenti M, et al. (1992) Pancreatic exocrine carcinoma producing adrenocorticotropic hormone. Pancreas 7(2): 172-176.

9 Delisle L, Boyer MJ, Warr D, Killinger D, Payne D, et al. (1993) Ectopic corticotropin syndrome and small-cell carcinoma of the lung. Clinical features, outcome, and complications. Arch Intern Med 153(6): 746-752.

10 Dimopoulos MA, Fernandez JF, Samaan NA, Holoye PY, Vassilopoulou-Sellin R (1992) Paraneoplastic Cushing's syndrome as an adverse prognostic factor in patients who die early with small cell lung cancer. Cancer 69(1): 66-71.

11 Shepherd FA1, Laskey J, Evans WK, Goss PE, Johansen E, et al. (1992) Cushing's syndrome associated with ectopic corticotropin production and small-cell lung cancer. J Clin Oncol 10: 21-27.

12 Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, et al. (1991) Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. N Engl J Med 325(13): 897-905.

13 Small Cell Lung Cancer Treatment (PDQ®)–Health Professional Version. NCI.

14 Kato A, Hayashi K, Naitoh I, Seno K, Okada Y, et al. (2016) Neuroendocrine carcinoma of the ampulla of Vater causing ectopic adrenocorticotropic hormone-dependent Cushing's syndrome. Mol Clin Oncol 5(1): 113-116.

15 Fujimoto K1, Nakashima T, Sasaki K, Hayashi K, Hanafusa M, et al. (2016) Ectopic adrenocorticotropic hormone syndrome caused by neuroendocrine carcinoma of the colon. Nihon Shokakibyo Gakkai Zasshi 113(10): 1752-1760.

16 Yao WQ, Wu X, Li GD, Wu WL, Wang WY (2015) ACTH-secreting pancreatic neuroendocrine carcinoma with ovarian and pelvic metastases causing Cushing's syndrome: a case report. Int J Clin Exp Pathol 8(11): 15396-15401.

17 Thoren M, Adamson U, Sjoberg HE (1985) Aminoglutethimide and metyrapone in the management of Cushing's syndrome. Acta Endocrinol (Copenh) 109(4): 451-457.

18 Verhelst JA, Trainer PJ, Howlett TA, Perry L, Rees LH, et al. (1991) Short- and long- term responses to metyrapone in the medical management of 91 patients with Cushing's syndrome. Clinical Endocrinology 35(2):169-178.

19 Winquist EW, Laskey J, Crump M, Khamsi F, Shepherd FA (1995) Ketoconazole in the management of paraneoplastic Cushing's syndrome secondary to ectopic adrenocorticotropin production. J Clin Oncol 13(1):157-164.

20 Bertagna X, Favrod-Coune C, Escourolle H, Beuzeboc P, Christoforov B, et al. (1989) Suppression of ectopic adrenocoticotropin secretion by the long-acting somatostatin analog octreotide. J Clin Endocrinol Metab 68(5): 988-991.

21 Hearn PR, Reynolds CL, Johansen K, Woodhouse NJY (1988) Lung carcinoid with Cushing's syndrome: control of serum ACTH and cortisol levels using SMS 201-995 (Sandostatin). Clinical Endocrinology 28(2): 181-185.

22 Farwell FP, Devlin JT, Stewart JA (1988) Total suppression of cortisol excretion by ketoconazole in the therapy of the ectopic adrenocorticotropic hormone syndrome. Am J Med 84(6): 1063-1066.

23 Sonino N (1987) The use of ketoconazole as an inhibitor of steroid production. N Engl J Med 317(13): 812-818.

Citation: Wells T, Day A, Hilman S (2016) Ectopic ACTH Production: Diagnosis, Treatment and Prognosis. J Cancer Prev Curr Res 6(3): 00208. DOI: 10.15406/jcpcr.2016.06.00208