Endocrinology, Diabetes & Metabolism CASE REPORTS

H Venugopal and others | A case of severe ectopic ACTH syndrome | ID: 15-0099; December 2015 DOI: 10.1530/EDM-15-0099

A case of severe ectopic ACTH syndrome from an occult primary – diagnostic and management dilemmas

Harish Venugopal, Katherine Griffin and **Saima Amer**

Department of Diabetes and Endocrinology, Gold Coast University Hospital, 1 Hospital Boulevard, Southport, QLD 4215 Queensland, Australia

Correspondence should be addressed to H Venugopal
Email
harish.venugopal@health.qld.gov.au or hv1979@hotmail.com

Summary

Resection of primary tumour is the management of choice in patients with ectopic ACTH syndrome. However, tumours may remain unidentified or occult in spite of extensive efforts at trying to locate them. This can, therefore, pose a major management issue as uncontrolled hypercortisolaemia can lead to life-threatening infections. We present the case of a 66-year-old gentleman with ectopic ACTH syndrome from an occult primary tumour with multiple significant complications from hypercortisolaemia. Ectopic nature of his ACTH-dependent Cushing's syndrome was confirmed by non-suppression with high-dose dexamethasone suppression test and bilateral inferior petrosal sinus sampling. The primary ectopic source remained unidentified in spite of extensive anatomical and functional imaging studies, including CT scans and Dotatate-PET scan. Medical adrenolytic treatment at maximum tolerated doses failed to control his hypercortisolaemia, which led to recurrent intra-abdominal and pelvic abscesses, requiring multiple surgical interventions. Laparoscopic bilateral adrenalectomy was considered but decided against given concerns of technical difficulties due to recurrent intra-abdominal infections and his moribund state. Eventually, alcohol ablation of adrenal glands by retrograde adrenal vein approach was attempted, which resulted in biochemical remission of Cushing's syndrome. Our case emphasizes the importance of aggressive management of hypercortisolaemia in order to reduce the associated morbidity and mortality and also demonstrates that techniques like percutaneous adrenal ablation using a retrograde venous approach may be extremely helpful in patients who are otherwise unable to undergo bilateral adrenalectomy.

Learning points:

- Evaluation and management of patients with ectopic ACTH syndrome from an unidentified primary tumour can be very challenging.
- Persisting hypercortisolaemia in this setting can lead to debilitating and even life-threatening complications and hence needs to be managed aggressively.
- Bilateral adrenalectomy should be considered when medical treatment is ineffective or poorly tolerated.
- Percutaneous adrenal ablation may be considered in patients who are otherwise unable to undergo bilateral adrenalectomy.

Background

An ectopic ACTH secreting tumour is an uncommon cause of Cushing's syndrome. Lungs are the most common sites for the primary tumour, which is usually a bronchial carcinoid or a small cell lung cancer (1). However, the primary tumour may remain unidentified in as many as 12–19% of the cases (2), (3). Management of these occult ectopic ACTH secreting tumours can often be difficult. Here, we present a case of severe ectopic ACTH syndrome and the difficulties we faced in its evaluation and management.

Case presentation

A 66-year-old gentleman was admitted under our care with a 6-month history of rapidly declining mobility with severe proximal muscle weakness and atrophy affecting both lower and upper limbs. A recent diagnosis of Cushing's syndrome had been made by his private physician on the basis of 24-h urinary-free cortisol levels and overnight low dose dexamethasone suppression test (LDDST). His private physician had also performed an MRI scan of the pituitary that had not revealed a pituitary adenoma. Other concerns at admission included multiple vertebral fractures, recently diagnosed and poorly controlled diabetes, skin bruises and recurrent urinary tract infections. He denied any exogenous glucocorticoid intake as a cause for his symptoms. On physical examination, the most striking features included significant wasting of the proximal muscles groups of both upper and lower limbs, and extensive skin bruising. He had mild central obesity, but no abdominal striae or dorso–cervical fat pad.

Investigations

His initial laboratory testing is shown in Table 1. Cushing's syndrome was confirmed on the basis of elevated 24-h urinary cortisol levels and failure to suppress cortisol with 1 mg overnight LDDST. Loss of circadian rhythm of cortisol secretion was also in favour of Cushing's syndrome. ACTH was elevated consistent with ACTH-dependent Cushing's syndrome, and failure to suppress cortisol on an 8-mg overnight high dose dexamethasone suppression test (HDDST) favoured a diagnosis of ectopic Cushing's syndrome. Pituitary CT scan showed normal pituitary gland. Similarly, CT scans of his neck, chest, abdomen and pelvis demonstrated no potential source of ectopic ACTH. Further evaluation with gallium-68 Dototate PET-CT scan was also unrevealing. Biochemical screening for other neuroendocrine tumours like carcinoid tumour (urinary 5-HIAA levels), phaeochromocytoma (plasma metanephrines) and medullary carcinoma thyroid (calcitonin) were negative. At this point, the possibility of Cushing's disease was reconsidered and bilateral inferior petrosal sinus sampling (BIPSS) with CRH stimulation was performed (Table 2), the results of which were consistent with ectopic ACTH production.

Treatment

Ketoconazole was initially commenced at a dose of 200 mg twice a day and subsequently increased to 400 mg twice a day. However, new derangement in liver function tests resulted in cutting back of the dose and eventual cessation following 2 weeks of treatment. Metyrapone was trialled subsequently at a starting dose of 250 mg three times a day. The dose was escalated following limited response; however, concerns of increasing peripheral oedema and

Table 1 Patient's biochemistry results.

Test	Time	Result	Normal range
Serum potassium	1500 h	3.0	3.5–5.1 mmol/l
Serum bicarbonate	1500 h	36	22–32 mmol/l
Serum cortisol	2230 h	1550	<50 nmol/l
Serum cortisol	0655 h	1480	200–700 nmol/l
Plasma ACTH	0655 h	110	20–50 ng/l
24-h urinary-free cortisol		3440	<150 nmol/24 h
Overnight LDDST			
	Basal, pre-dose	1550 nmol/l	
	Post-dose (1 mg)	1480 nmol/l	
Overnight HDDST	Basal, pre-dose	1480 nmol/l	
	Post-dose (8 mg)	1110 nmol/l	

ACTH, adrenocorticotropic hormone; LDDST, low dose dexamethasone suppression test; HDDST, high dose dexamethasone suppression test.

Table 2 Inferior petrosal sinus sampling.

	ACTH (ng/l)		
Time	Left petrosal	Right petrosal	Peripheral
Basal 1	93	97	13
Basal 2	100	99	83
2 min	98	98	85
5 min	100	100	91
10 min	100	100	82

ACTH, adrenocorticotropic hormone.

worsening hypertension led to the dose being cut back to 250 mg three times a day. We were unable to consider other cortisol lowering treatments like etomidate and mifepristone (glucocorticoid receptor blocker) due to issues with availability of these medications in Australia. Persisting severe hypercortisolaemia and immunocompromised state led to recurrent sepsis from intra-abdominal infections including bowel perforation and pelvic abscesses. These required multiple surgical interventions including Hartmann's procedure and colostomy. Specific microbial infections included multi-drug resistant strains of *Escherichia coli*, *Klebsiella* and *Candida* requiring prolonged and multiple courses of broad-spectrum antibiotics. The patient also developed heart failure and atrial fibrillation. Laparoscopic bilateral adrenalectomy was discussed with the endocrine surgeons as a means to control his hypercortisolaemia; however, the surgical risk was deemed too high due to the recurrent intra-abdominal infections and recent surgery and the patient's moribund state. As a last resort, percutaneous adrenal ablation under radiological guidance was attempted. An initial attempt at direct injection into the adrenal gland with ethanol was unsuccessful. A second attempt with a retrograde venous approach and ethanol embolization was met with better success. Catheters were initially inserted in the common femoral veins and subsequently advanced into the renal veins and then into the adrenal veins. Ethanol mixed with contrast was then injected into the adrenal veins. Retrograde venous ablation resulted in successfully ablating the left adrenal (by inducing thrombosis) but only partially on the right side as the procedure had to be terminated early due to intra-operative hypertension.

Outcome and follow-up

This procedure did not result in inducing complete hypoadrenalism immediately, but did significantly reduce the cortisol levels (Table 3). Metyrapone was therefore continued, but hydrocortisone was initiated as part of 'block and replace' therapy. Following the procedure, the patient remained well and did not suffer any further infections. He was subsequently considered for rehabilitation and made reasonable gains in spite of significant deconditioning and muscle wasting (from prolonged hypercortisolaemia and hospitalization). Repeat CT scan of his chest, abdomen and pelvis 6 months following adrenal ablation again revealed no malignant focus. Treatment with metyrapone was eventually ceased 12 months after adrenal ablation. He now remains on hydrocortisone at physiological replacement doses with cortisol levels well within the normal range. He currently lives semi-independently in a nursing home and mobilises with a wheelie walker. He manages an extensive social life and has a good quality of life. He also continues being followed up in our clinic with yearly screening CT scan of his chest, abdomen and pelvis.

Discussion

This case illustrates the challenges in evaluation of patients with ectopic ACTH syndrome (EAS) especially where a primary tumour has not yet been identified. Persisting hypercortisolaemia in this setting can lead to debilitating and even life-threatening complications and hence needs to be managed aggressively. The most common source of ectopic ACTH secretion is the lung, either from a bronchial carcinoid or small cell lung cancer (1). Rarely, it can also occur in other neuroendocrine tumours (NET) including medullary carcinoma thyroid, phaeochromocytoma, thymic carcinoid and pancreatic NETs, and prostate cancers. EAS can be diagnosed biochemically by demonstrating non-suppressibility with a high dose DST; however, it must be borne in mind that the sensitivity and specificity of this test is not 100% (4), and hence, if imaging with CT or MRI, and functional studies such as octreotide scintigraphy do not

Table 3 Post-treatment results.

			Following adrenal ablation			
	Pre-treatment	**With maximal medical treatment**	After 2 weeks	After 1 year	After 18 months	**Normal range**
Serum cortisol	1480 (0655 h)	985 (0755 h)	341 (0600 h)	20 (0730 h)	150 (0800 h)	200–700 nmol/l
24-h urinary-free cortisol	3440	1040	111	120	220	< 150 nmol/24 h

ID: 15-0099; December 2015
DOI: 10.1530/EDM-15-0099

demonstrate a tumour, the diagnosis of EAS should be questioned and Cushing's disease should be reconsidered. Typically, in EAS, the degree of ACTH hypersecretion and excretion of urinary free cortisol is much higher than compared to Cushing's disease. CRH stimulation usually results in increase in ACTH and cortisol levels in Cushing's disease, but not in EAS. The HDDST when combined with CRH stimulation test usually differentiates EAS from Cushing's disease reasonably well however can still miss a few cases of Cushing's disease. BIPSS is generally considered the gold standard test for differentiating Cushing's disease from EAS. This should be considered in all patients when the primary tumour has not been identified (5). Absence of a central to peripheral ACTH gradient confirms an ectopic source of ACTH secretion. Rarely, false negatives can occur with BIPSS and are related to incorrect catheter placement or anomalous venous drainage or anatomy.

There is no optimal strategy for detecting ectopic ACTH secreting tumours, although it may be cost-effective to start by imaging the chest, as most ACTH secreting tumours are located there, and then proceed to image other regions as necessary. CT and MRI are anatomical scans that locate most tumours; however, functional studies in the form of somatostatin receptor scintigraphy or PET scans may be required where tumours remain undetected. Functional studies including octreotide or pentetreotide scintigraphy or Gallium-68 Dototate PET-CT scan use tracers to target somatostatin receptors, (SSR types 2 and 5) which are expressed on the cell-surface of most neuroendocrine tumours making them easy to identify. Although scintigraphy may be helpful in demonstrating the functional nature of the tumour, it does not provide good resolution and needs to be correlated with a CT or MRI. Gallium-68 Dototate PET-CT scan has demonstrated high sensitivity for identification of neuroendocrine tumours, which account for majority of the ectopic ACTH secreting tumours. It can, therefore, play a major role in detecting these tumours. 18-FDG PET CT has limited application in detecting neuroendocrine tumours, especially carcinoid, due to their limited metabolic activity; has a sensitivity of only around 66% for detecting neuroendocrine tumours and hence is not routinely used (6).

A small proportion of tumours remain occult despite thorough investigation and it should be noted that where the primary tumour is not found, the risk of morbidity and mortality is more likely to occur secondary to hypercortisolaemia as opposed to the primary malignancy, and if the hypercortisolaemia is corrected, the prognosis is generally favourable (1). When the ectopic tumour is identified, surgical resection is the ideal treatment. In patients with single primary lesion, curative resection was found to be successful in 82% of cases (2); however, until the time the patient is ready for surgery, or in cases of occult tumour, medical treatment to lower cortisol levels should be initiated without delay. The common adrenolytic treatments that may be considered include metyrapone, ketoconazole or mitotane. Etomidate is an option that can be given intravenously to rapidly control cortisol levels in emergency situations (1). Mifepristone is a glucocorticoid receptor antagonist that may also be trialled. These adrenolytic treatments are associated with severe side effects that may limit their use. Bilateral (or even unilateral) adrenalectomy may be considered when medical treatment is ineffective, poorly tolerated or rejected by the patient, in young women desiring pregnancy or when the ectopic source is unresectable or occult. Bilateral adrenalectomy has been shown to substantially improve the quality of life by relieving the symptoms and signs of Cushing's syndrome (7). A laparoscopic approach is preferable because of associated lower morbidity and mortality compared to an open approach (7).

For patients who are not medically fit to withstand surgery (or decline to have surgery), percutaneous adrenal ablation may be considered. The various methods available include radiofrequency ablation, cryoablation, microwave and chemical ablation. Chemical ablation can be done percutaneously either by injecting alcohol or acetic acid directly into the adrenal gland or embolization of the adrenal artery (8). Our patient failed direct injection of ethanol into the adrenal gland, following which we adopted a retrograde venous approach with reasonably good effect. To our knowledge, retrograde venous adrenal ablation has been reported only once in literature (9), making our case the second. Patients should ideally be screened for hormone secreting adrenal tumours like phaeochromocytomas before the procedure. Even in the absence of phaeochromocytomas, they should be appropriately alpha- and beta-blocked beforehand to avoid hypertensive crisis during this procedure. Other complications of percutaneous ablation include bleeding and infection and thermal injury to nearby structures (if thermal ablation attempted) (8). Endoscopic bilateral adrenalectomy has been reported in one case series of EAS by Alberda *et al* (10) as an option in patients not medically fit for even laparoscopic bilateral adrenalectomy.

In summary, evaluation and management of ectopic ACTH syndrome can be very challenging and our case emphasizes the importance of aggressive management of

hypercortisolaemia in order to reduce the associated morbidity and mortality. Medical adrenolytic treatments are generally first line; however, bilateral adrenalectomy may be necessary, and can be life saving, when medical treatment fails. We have demonstrated that percutaneous adrenal ablation using a retrograde venous approach is a technique that can be considered in patients who are otherwise unable to undergo bilateral adrenalectomy.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding
This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Patient consent
Written informed consent has been obtained from the patient for publication of the case report.

Author contribution statement
Dr H Venugopal is a Consultant Endocrinologist who looked after the patient while training as an Advanced Trainee in Endocrinology. He also wrote the initial draft of this manuscript. Dr K Griffin and Dr S Amer are Consultant Endocrinologists who were the named physicians responsible for the patient's care at different times. They also reviewed and revised this manuscript.

References

1 Grossman AB, Kelly P, Rockall A, Bhattacharya S, McNicol A & Balwick T 2006 Cushing's syndrome caused by an occult source: difficulties in diagnosis and management. *Nature Clinical Practice. Endocrinology & Metabolism* **2** 642–647. (doi:10.1038/ncpendmet0327)

2 Isidori AM, Kaltsas GA, Pozza C, Frajese V, Newell-Price J, Reznek RH, Jenkins PJ, Monson JP, Grossman AB & Besser GM 2006 The ectopic adrenocorticotrophin syndrome: clinical features, diagnosis, management and long-term follow-up. *Journal of Clinical Endocrinology and Metabolism* **91** 371–377. (doi:10.1210/jc.2005-1542)

3 Ilias I, Torpy DJ, Pacak K, Mullen N, Wesley RA & Nieman LK 2005 Cushing's syndrome due to ectopic corticotropin secretion: twenty years' experience at the National Institutes of Health. *Journal of Clinical Endocrinology and Metabolism* **90** 4955–4962. (doi:10.1210/jc.2004-2527)

4 Dichek HL, Nieman LK, Oldfield EH, Pass HI, Malley JD & Cutler GB, Jr 1994 A comparison of the standard high dose dexamethasone suppression test and the overnight 8-mg dexamethasone suppression test for the differential diagnosis of adrenocorticotropin-dependent Cushing's syndrome. *Journal of Clinical Endocrinology and Metabolism* **78** 418–422. (doi:10.1210/jcem.78.2.8106630)

5 Oldfield EH, Doppman JL, Nieman LK, Chrousos GP, Miller DL, Katz DA, Cutler GB, Jr & Loriaux DL 1991 Petrosal sinus sampling with and without corticotropin-releasing hormone for the differential diagnosis of Cushing's syndrome. *New England Journal of Medicine* **325** 897. (doi:10.1056/NEJM199109263251301)

6 Venkitaraman B, Karunanithi S, Kumar A, Bal C, Ammini AC & Kumar R 2014 ^{68}Ga-DOTATOC PET-CT in the localization of source of ectopic ACTH in patients with ectopic ACTH-dependent Cushing's syndrome. *Clinical Imaging* **38** 208–211. (doi:10.1016/j.clinimag.2013.10.007)

7 Salameh JR, Borman KR & Varkarakis GM 2008 Laparoscopic bilateral adrenalectomy for occult ectopic ACTH syndrome. *Journal of Laparoendoscopic & Advanced Surgical Techniques. Part A* **18** 52–55. (doi:10.1089/lap.2007.0016)

8 Venkatesan AM, Locklin J, Dupuy DE & Wood BJ 2010 Percutaneous ablation of adrenal tumors. *Techniques in Vascular and Interventional Radiology* **13** 89–99. (doi:10.1053/j.tvir.2010.02.004)

9 Gatti A, Baroni MG, Romeo S, Mandosi E, Fallarino M, Bezzi M, Paciucci L, Filetti S & Morano S 2008 A case of severe occult ectopic adrenocorticotropin syndrome treated with retrograde venous adrenal ablation using ethanol. *Journal of Endocrinological Investigation* **31** 1135–1136. (doi:10.1007/BF03345665)

10 Alberda WJ, van Eijck CH, Feelders RA, Kazemier G, de Herder WW & Burger JW 2012 Endoscopic bilateral adrenalectomy in patients with ectopic Cushing's syndrome. *Surgical Endoscopy* **26** 1140–1145. (doi:10.1007/s00464-011-2020-7)

Received in final form 9 October 2015
Accepted 11 November 2015