Journal of the ASEAN Federation of Endocrine Societies

CASE REPORT

A Difficult Case of Ectopic ACTH Syndrome: Is Treatment Possible Even Without Accurate Localization?

Adam I Kaplan,[1,2] Liam Clifford,[1] Ammar Wakil[3]

[1]*Department of Endocrinology, Gosford Hospital, Gosford, New South Wales, Australia*
[2]*School of Medicine and Public Health, The University of Newcastle, New South Wales, Australia*
[3]*Department of General Medicine, Wyong Hospital, Wyong. New South Wales, Australia*

Abstract

Occult ectopic adrenocorticotropic hormone (ACTH) syndrome (EAS) is a relatively rare form of ACTH-dependent Cushing's Syndrome (CS). We describe a middle-aged female with symptomatic CS, where despite thorough investigations including hormone suppression testing, multiple imaging modalities, and inferior petrosal sinus sampling (IPSS), an ectopic source could not be demonstrated. Our case demonstrates that ketoconazole can be an effective therapeutic to suppress cortisol production even when the source of ectopic ACTH production is unknown. However, long-term evaluation is required.

Key words: ectopic ACTH syndrome, Cushing syndrome, hypercortisolism, ketoconazole

INTRODUCTION

Ectopic adrenocorticotropic hormone (ACTH) Syndrome (EAS) accounts for up to 12% of all Cushing's Syndrome (CS)[1], and 10-20% of ACTH dependent CS cases.[2] Removal of the ectopic ACTH source results in potential cure and resolution of the excess cortisol production, and improvement in the sequelae.[3] Improved imaging techniques have shown a wide spectrum of malignancies associated with EAS, with the most frequent aetiology being neuroendocrine tumours (NET).[2] Localising the ectopic source of ACTH can be difficult, and if untreated, it can have a significant impact on morbidity and mortality. Up to 20% of EAS cases do not have a lesion identified, even after long-term monitoring.[2,4] The currently recorded prevalence is approximately 12%, with a risk of malignancy. It is necessary to detect and monitor the effects of therapy and prevent the unpredictable risk of recurrence. This case explores occult EAS and the challenges encountered when the primary lesion cannot be identified.

CASE

A 62-year-old female had recurrent hospital presentations due to dyspnoea, lower limb oedema and reduced mobility with falls. She was being treated for heart failure with preserved ejection fraction (HFpEF), with a past medical history of hypertension, hypercholesterolaemia, type-II diabetes mellitus, obesity, functional neurological disorder, generalised anxiety disorder, and prior thyroidectomy. Her medications included apixaban 5 mg BD, empagliflozin 10 mg mane, frusemide 80 mg BD, hydrochlorothiazide 12.5 mg mane, insulin aspart 30-units TDS, insulin glargine 75-units nocte, metformin MR 500 mg BD, metoprolol 25 mg BD, simvastatin 80 mg nocte, spironolactone 25 mg mane, and thyroxine 150 mcg daily. She also presented with hyperglycaemia, recurrent severe hypokalaemia and worsening mental health.

Physical examination revealed moderate hypertension, Cushingoid features such as facial roundness and central adiposity, and fluid overload. She had never been on a prolonged course of a corticosteroid and had no family history of NET or CS.

Her midnight serum cortisol was elevated at 506 nmol/L with elevated ACTH 95.1 ng/L (7.2-63.3), elevated 24-hour urine free cortisol 1411 nmol (<270), and elevated salivary cortisol 37 nmol/L (<8). Cortisol was not sufficiently suppressed with overnight high-dose 8 mg dexamethasone, suggestive of ectopic ACTH production. Endocrine biochemistry and baseline renal and liver function are summarised in Table 1.

CT imaging of the adrenal glands demonstrated a 15 x 13 mm nodule in the lateral limb of the left adrenal (unchanged in size in two years) with <10 Hounsfield units (HU), consistent with a left benign adrenal lipoma. The medial limb was bulky in appearance, measuring 12 x 11 mm with a focal low-density nodule of <10 HU, radiologically considered to represent another adrenal adenoma, also

eISSN 2308-118x (Online)
Printed in the Philippines

Received: February 8, 2025. Accepted: April 23, 2025.
Published online first: November 3, 2025.
https://doi.org/10.15605/jafes.040.02.26

Corresponding author: Adam I Kaplan, BSc (Adv), MD
Resident Medical Officer
Department of Endocrinology, Gosford Hospital,
Gosford, New South Wales, 2250, Australia
E-mail: adam.kaplan@health.nsw.gov.au
ORCiD: https://orcid.org/0000-0001-5824-2991

Table 1. Baseline hormonal panel and cortisol testing

Test	Results[β]	Laboratory reference range
Body weight	110.9 kg	-
Morning serum cortisol	764 nmol/L	100 - 535
Midnight serum cortisol	506 nmol/L	<206
Serum ACTH	95.1 ng/L	7.2 - 63.3
24-hr urine free cortisol	1411 nmol/24hr	<270
Midnight salivary cortisol	37 nmol/L	<8
Cortisol pre-dexamethasone[α]	942 nmol/L	100 - 535
Cortisol post-dexamethasone[α]	560 nmol/L	<50
Fasting glucose	13.2 mmol/L	3.0 - 5.4
HbA1c	75 mmol/mol (9.1%)	23 - 43 (4.0 - 6.0)
Total daily insulin (exogenous)	165 units	-
TSH	0.98 mIU/L	0.40 - 4.00
FT4	14.9 pmol	9.0 - 19.0
Chromogranin A	133.5 ng/mL	0.0 - 101.9
Growth hormone	<0.1 ug/L	<8.0
FSH	0.3 IU/L	26.7 - 133
LH	<0.2 IU/L	5.2 - 62.0
Prolactin	176 mIU/L	110 - 560
IGF-1	11.4 nmol/L	7.0 - 27.0
eGFR	>90 mL/min/1.73 m^2	>90
Creatinine	61 umol/L	45 - 90
Bilirubin	8 umol/L	<20
Alanine aminotransferase	53 u/L	10 - 35
Aspartate aminotransferase	45 u/L	10 - 35
Alkaline phosphatase	38 u/L	30 - 110
Gamma-glutamyl transferase	553 u/L	5 - 35

[α] 8 mg overnight dexamethasone suppression test
[β] Baseline results compiled from various hospital presentations over 2022–2023

unchanged from previous imaging. Right adrenal gland was unremarkable. Pituitary MRI demonstrated a 2 mm area of hypoenhancement in the posterior portion of the pituitary, suggesting a possible pituitary microadenoma. Due to suspicion for hypercortisolaemia of pituitary origin, inferior petrosal sinus sampling (IPSS) was done, which demonstrated low central peripheral ACTH gradients in both basal conditions and following corticotrophin-releasing hormone administration, with ratios of <2 and <3, respectively. This was suggestive of ectopic (non-pituitary) ACTH production.

To search for an ectopic source including possible NET, CT chest/abdomen/pelvis and 187 MBq Ga68 DOTATATE PET scan were conducted, which demonstrated a 14-15 mm non-enhancing and non-avid left lingula nodule and known benign left adrenal lesion (non-avid), with no definite DOTATATE-avid lesion identified. In the absence of an identified NET, a biopsy of the lingula nodule was done, which demonstrated unremarkable alveolar lung tissue with negative ACTH histology. Finally, a nuclear medicine bone scan demonstrated no bone metastases.

She was diagnosed with occult ectopic CS. Due to financial inaccessibility of metyrapone, she was commenced on ketoconazole 200 mg BD (subsequently increased to 300 mg BD). This resulted in significant biochemical improvement with a reduction in 24-hour urine free cortisol (453 nmol after 2-weeks of therapy; 41 nmol after 2 months) and a significantly suppressed cortisol following overnight dexamethasone testing after one week of ketoconazole (cortisol levels: 456 nmol/L pre-dexamethasone; 43 nmol/L post-dexamethasone). Serum (morning) cortisol levels before and after ketoconazole therapy are illustrated in Figure 1.

Most recent follow-up results are summarised in Table 2, demonstrating continued efficacy of ketoconazole. The patient continues to be monitored by an endocrinologist, with ongoing biochemical and imaging surveillance. The patient management plan involves continuous investigation of the underlying cause of ectopic ACTH production, with the aim of cure when its location becomes apparent.

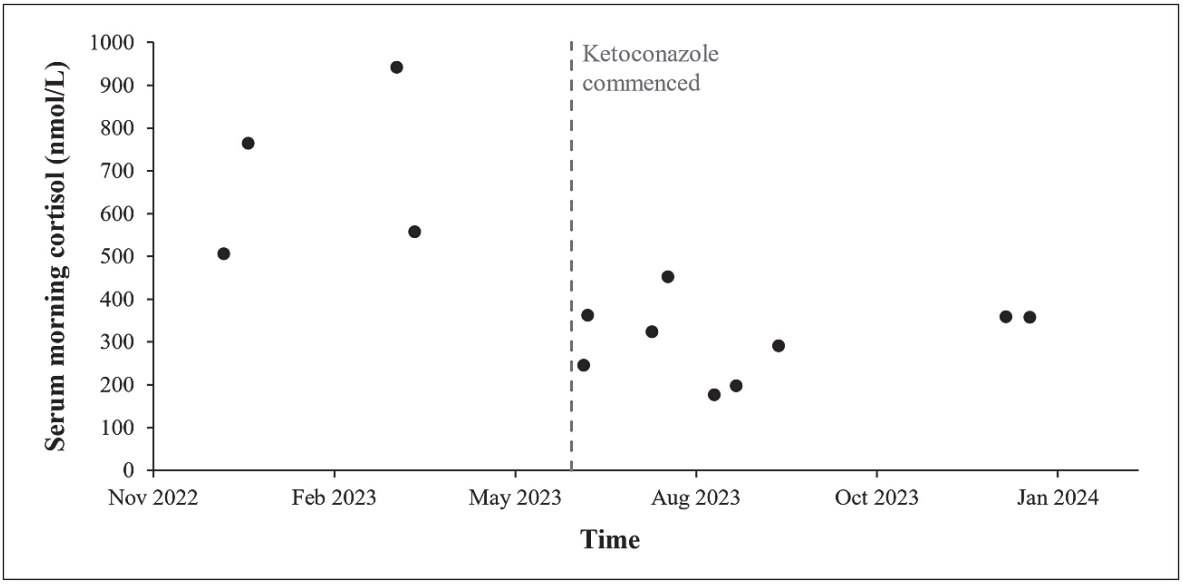

Figure 1. Serum morning cortisol (nmol/L) concentrations over time from initial presentation to January 2024. The commencement of ketoconazole is illustrated by the dashed grey vertical lines.

Table 2. Biochemistry results after 7 months of continuous ketoconazole therapy

Test	Result	Laboratory reference range
Body weight	90 kg	-
24-hour urine free cortisol	88 nmol/24 hr	<270
Morning serum cortisol	358 nmol/L	100 - 535
Serum ACTH	57 ng/L	7.2 – 63.3
Fasting glucose	9.2 mmol/L	3.0 – 5.4
HbA1c	41 mmol/mol (5.8%)	23 – 43 (4.0 - 6.0)
Total daily insulin (exogenous)	78 units	-
TSH	6.41 mIU/L	0.40 - 4.00
FT4	17.2 pmol/L	9.0 - 19.0
eGFR	73 mL/min/1.73 m^2	>90
Creatinine	71 umol/L	45 - 90
Bilirubin	16 umol/L	<20
Alanine aminotransferase	27 u/L	10 - 35
Aspartate aminotransferase	28 u/L	10 - 35
Alkaline phosphatase	91 u/L	30 - 110
Gamma-glutamyl transferase	488 u/L	5 - 35

DISCUSSION

EAS presents a complex diagnostic and therapeutic challenge to clinicians. Thorough and targeted clinical history taking and examination remain paramount to initial assessment. Several clinical signs of hypercortisolism may be missed, therefore, if there is high suspicion for hypercortisolism, clinical examination should investigate for signs such as central adiposity, rounded face, dorsocervical fat pad, proximal myopathy, cutaneous striae, and thinning of skin among others. Distinction between EAS and pseudo-Cushing's states such as obesity, chronic alcohol misuse, polycystic ovarian syndrome and psychiatric disorders where there is activation of the hypothalamus-pituitary adrenal-axis, can be difficult on history and examination alone; targeted dynamic hormonal testing may assist further diagnosis.[5]

An important distinguishing feature of EAS from other forms of CS is the presentation of symptoms – muscle weakness as the most common, followed by hypertension, infections and peripheral oedema. Intriguingly, it has been found that weight loss is more prevalent than weight gain[3] and hypokalaemia is often present as demonstrated in our case.[6] The onset of predominant mineralocorticoid signs should signal a high degree of suspicion for EAS.[7] It has been found that an ACTH level >148 pmol/L is more indicative of EAS than CS.[8] The gold standard for diagnosing EAS is IPSS, which allows for the differentiation of the ACTH excess - either from a pituitary to an ectopic source.[9] Once EAS is diagnosed, a combination of different modality techniques, including a DOTATATE and PET/CT, are important for localising the source.[10]

Treatment of occult EAS often involves control of hypercortisolaemia through use of adrenal steroidogenesis inhibitors such as ketoconazole and metyrapone, glucocorticoid receptor antagonist such as mifepristone, or bilateral adrenalectomy in patients with severe hypercortisolism where medical control of CS is not feasible.[11] In our case, the patient responded well to ketoconazole. Ketoconazole is effective due to enzyme inhibition involved in cortisol synthesis. However, due to the rare hepatotoxicity risk with oral ketoconazole use, regular monitoring of liver enzyme levels is recommended.[8] If identified, the definitive treatment is resection of the causative tumour, however other therapies may include chemotherapy, radiotherapy, or a long-acting somatostatin analogue.[3] In refractory cases of occult EAS, bilateral adrenalectomy can be considered for cure of CS, however, the underlying ectopic source of ACTH remains. Due to the biochemical success and patient tolerance of continued medical therapy, surgical risks involved in bilateral adrenalectomy, lifelong glucocorticoid and mineralocorticoid replacement, and patient preference for non-surgical management pending identification of the underlying ectopic source, adrenalectomy was not undertaken in this case.

Management of occult EAS is seldom reported in the literature, though published cases have highlighted the difficulty of managing occult EAS. One similar case initially tried ketoconazole, however therapy was ceased after 2 weeks due to new liver enzyme derangement.[12] The patient was then commenced on metyrapone before eventually requiring urgent percutaneous adrenal ablation as salvage therapy in the setting of severe refractory hypercortisolemia with the patient not deemed fit for laparoscopic bilateral adrenalectomy. Another case of occult EAS was presented by Cannon and Doherty.[13] Similarly, ketoconazole therapy was initially used while investigating the source of ectopic production, resulting in a reported 50% reduction in cortisol levels. However, due to suspicion of an intra-abdominal ectopic source, the authors undertook surgical exploration with intraoperative ultrasonography, identifying a pancreatic neuroendocrine tumor with metastatic disease. Distal pancreatectomy, splenectomy and left adrenalectomy were undertaken. Due to persistently elevated ACTH, right adrenalectomy was additionally required, with subsequent glucocorticoid and mineralocorticoid replacement therapy. Compared to these cases, our patient remains stable on medical management and we plan to continue surveillance with periodic imaging.

Additionally, the combination of type 2 diabetes mellitus accompanied by central obesity in middle-aged and elderly patients can be suspicious for hypercortisolism, which further worsens pre-existing diabetes. Use of exogenous insulin, an anabolic hormone, is associated with weight gain which increases cardiovascular complications, particularly in patients with metabolic syndrome. In patients with type 2 diabetes where weight loss would be medically beneficial, therapy with GLP-1 receptor agonists should be considered.[14]

Compared to computed tomography and magnetic resonance imaging, DOTATATE and PET/CT scans provide a higher degree of sensitivity and specificity, and are

often able to identify lymph node and bone metastases.[2] Peptide receptor radionuclide therapy is a novel management option for EAS, and the aforementioned imaging modalities can help indicate if this will be effective as evidenced by considerable uptake in the tumour burden.[2,3]

CONCLUSION

Occult EAS is an important subset of CS which presents a diagnostic and management dilemma for physicians. This case demonstrates a methodical investigation of hypercortisolaemia, highlighting the difficulty of localising an ectopic source of ACTH. Ultimately, this case demonstrates a strong biochemical response to ketoconazole treatment in the absence of ectopic identification.

Ethical Consideration
Patient consent forms were obtained before manuscript submission.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
AIK: Conceptualization, Methodology, Formal analysis, Writing – original draft preparation, Writing – review and editing, Visualization; **LC:** Conceptualization, Methodology, Formal analysis, Writing – original draft preparation, Writing – review and editing, Supervision; **AW:** Conceptualization, Methodology, Formal analysis, Writing – review and editing, Supervision.

Data Availability Statement
No datasets were generated or analyzed for this study.

Author Disclosure
The authors declared no conflict of interest.

Funding Source
None.

References
1. Lindsay JR, Nieman LK. Differential diagnosis and imaging in Cushing's syndrome. Endocrinol Metab Clin North Am. 2005;34(2): 403-21. PMID: 15850850 DOI: 10.1016/j.ecl.2005.01.009
2. Hayes A, Grossman A. Distinguishing Cushing's disease from the ectopic ACTH syndrome: Needles in a haystack or hiding in plain sight? J Neuroendocrinol. 2022;34(8):e13137. PMID: 35980277 PMCID: PMC9542389 DOI: 10.1111/jne.13137
3. Palen-Tytko J, Przybylik-Mazurek E, Rzepka E, et al. Ectopic ACTH syndrome of different origin - Diagnostic approach and clinical outcome. Experience of one clinical centre. PLoS One. 2020; 15(11):e0242679. PMID: 33237923 PMCID: PMC7688153 DOI: 10.1371/journal.pone.0242679
4. Isidori A, Sbardella E, Zatelli M; ABC Study Group. Conventional and nuclear medicine imaging in ectopic Cushing's syndrome: A systematic review. J Clin Endocrinol Metab. 2015;100(9):3231-44. PMID: 26158607 PMCID: PMC4570166 DOI: 10.1210/JC.2015-1589
5. Scaroni C, Albiger NM, Palmieri S, et al. Approach to patients with pseudo-Cushing's states. Endocr Connect. 2020;9(1):R1-13. PMID: 31846432 PMCID: PMC6993268 DOI: 10.1530/EC-19-0435
6. Castro M, García N, Pardo J, Alvarez C, Grao L, García J. Ectopic Cushing syndrome: Report of 9 cases. Endocrinol Diabetes Nutr (Engl Ed). 2018;65(5):255-64. PMID: 29655957 DOI: 10.1016/j.endinu.2018.02.001
7. Fernandez LG, Montenegro A, Torrecilla N, et al. Ectopic Cushing's syndrome: Clinical, diagnostic, treatment and follow up outcomes of 12 cases of lung ectopic ACTH. Endocrinol Diabetes Metab Case Rep. 2023:2023(2):22-0378. PMCID: PMC10266431 DOI:10.1530/EDM-22-0378
8. Lawrence L, Zhang P, Choi H, et al. A unique case of ectopic Cushing's syndrome from a thymic neuroendocrine carcinoma. Endocrinol Diabetes Metab Case Rep. 2019:2019:19-0002. PMID: 30802210 PMCID: PMC6391898 DOI: 10.1530/EDM-19-0002
9. Smushkin G, Phillips R, Chausse G. The elusive neuroendocrine tumor: Finding the ectopic ACTH source 16 years after the diagnosis of cushing syndrome. JCEM Case Rep. 2023;1(1):luac035. PMID: 37908269 PMCID: PMC10578410 DOI: 10.1210/jcemcr/luac035
10. Li B, Yan Z, Huang H. Case report: An unusual case of ectopic ACTH syndrome caused by mediastinal paraganglioma. Front Endocrinol (Lausanne). 2022;12:790975. PMID: 35069444 PMCID: PMC8769203 DOI: 10.3389/fendo.2021.790975
11. Alba EL, Japp EA, Fernandez-Ranvier G, et al. The Mount Sinai clinical pathway for the diagnosis and management of hypercortisolism due to ectopic ACTH syndrome. J Endocr Soc. 2022;6(7):bvac073. PMID: 35668997 PMCID: PMC9155620 DOI: 10.1210/jendso/bvac073
12. Venugopal H, Griffin K, Amer S. A case of severe ectopic ACTH syndrome from an occult primary - diagnostic and management dilemmas. Endocrinol Diabetes Metab Case Rep. 2015;2015:150099. PMID: 26649179 PMCID: PMC4671324 DOI: 10.1530/EDM-15-0099
13. Cannon J, Doherty GM. A case of occult ectopic adrenocorticotropic hormone-secreting tumor: Diagnostic and management dilemmas. Endocr Pract. 2008;14(5):588-91. PMID: 18753102 DOI: 10.4158/EP.14.5.588
14. Samson SL, Vellanki P, Blonde L, et al. American association of clinical endocrinology consensus statement: Comprehensive type 2 diabetes management algorithm - 2023 update. Endocr. Pract. 2023;29(5): 305-40. PMID: 37150579 DOI: 10.1016/j.eprac.2023.02.001