CASE REPORT

Ectopic ACTH syndrome complicated by multiple opportunistic infections treated with percutaneous ablation of the adrenal glands

Chrystal Chan,[1] James Mark Roberts[2]

[1]Department of Medicine, University of British Columbia, Vancouver, Canada
[2]Department of Medicine, University of British Columbia, Vancouver, Canada

Correspondence to
Dr Chrystal Chan,
chrystal.chan@gmail.com

Accepted 3 November 2017

SUMMARY

Ectopic adrenocorticotropic hormone (ACTH)-related Cushing's syndrome can lead to multiple complications including severe immunosuppression. If the ACTH-secreting tumour cannot be found, definitive treatment is surgical adrenalectomy, typically followed by glucocorticoid replacement. Here, we present a case of fulminant respiratory failure secondary to coinfection with *Pneumocystis jirovecii* and cytomegalovirus in a patient with ectopic ACTH-dependent Cushing's syndrome with occult primary. Due to significant deconditioning, she was unable to undergo definitive adrenalectomy and instead underwent percutaneous microwave ablation of the adrenal glands.

BACKGROUND

The incidence of endogenous Cushing's syndrome is estimated to be 0.2–5.0 per million people per year.[1] Approximately 80% of cases are adrenocorticotropic hormone (ACTH) dependent and are predominantly secondary to pituitary corticotroph adenoma (Cushing's disease).[1] Ectopic ACTH-producing tumours account for 5%–10% of cases of Cushing's syndrome and are most often small cell lung carcinomas or neuroendocrine tumours of the lung, thymus and pancreas. Up to 20% of ACTH tumours remain occult.[1] In these cases, bilateral surgical adrenalectomy is the definitive treatment.[2]

Cushing's syndrome is associated with increased multisystem morbidity including increased risk of myocardial infarction, stroke, venous thromboembolism, pathological fractures and opportunistic infections.[3] The mortality rate is approximately double that of the general population, predominantly related to an increase in cardiovascular risk factors.[1 3]

We present a case of Cushing's syndrome secondary to ectopic ACTH production with an occult primary. Her course was complicated by fulminant respiratory failure from coinfection with two opportunistic pathogens. This represents an uncommon but devastating complication of a well-known disease that may have possibly been prevented with prophylactic antimicrobials. Her subsequent frailty prohibited her from undergoing definitive surgical adrenalectomy. She was instead treated successfully with percutaneous ablation of the adrenal glands, a procedure that is presently used almost exclusively for adrenal tumours, but may possibly have a larger role in ectopic ACTH-related Cushing's syndrome in the future.

CASE PRESENTATION

A 63-year-old woman presented to her family doctor reporting a 1-month history of weakness, weight gain, headache and facial plethora. Her medical history included hypertension, dyslipidaemia and obstructive sleep apnoea. Examination revealed an overweight Chinese woman with a blood pressure of 183/117 mm Hg and a heart rate of 85 bpm. She was noted to have central obesity with abdominal striae, a cervicodorsal fat pad, facial hair, thin skin without bruising and mild proximal muscle weakness. Initial laboratory investigations were significant for a potassium level of 2.9 mmol/L, sodium level of 149 mmol/L and fasting glucose level of 11.4 mmol/L. She was started on spironolactone and referred to an endocrinologist. Subsequent outpatient work-up revealed an ACTH of 52.6 pmol/L (normal range 1.6–13.9 pmol/L) and morning cortisol of >1625 nmol/L after 1 mg dexamethasone challenge (see table 1 for normal values). Twenty-four-hour urinary free cortisol (UFC) measured >2622 nmol/day and was approximated to be ~16 000 nmol/day. Her aldosterone level was suppressed at <50 pmol/L (normal range 70–660 pmol/L). She was diagnosed with ectopic ACTH-dependent Cushing's syndrome and was admitted to the internal medicine service for work-up.

INVESTIGATIONS

In-hospital morning cortisol was 3319 nmol/L. Following an 8 mg dexamethasone suppression test, morning cortisol remained elevated at 3470 nmol/L. MRI of the head did not reveal any pituitary abnormalities. CT of chest, abdomen and pelvis revealed marked bilateral adrenal hyperplasia but no discrete lesions representing an adenoma or carcinoma (figure 1). PET scan revealed bilateral adrenal hyperplasia and hypermetabolism but no primary tumour. There was no octreotide receptor avid disease on indium 111 octreotide scan. Inferior petrosal sinus sampling was considered; however, given the magnitude of ACTH elevation and lack of pituitary abnormalities on MRI, in consultation with the neurosurgery service and the patient herself, the risk of the procedure outweighed the benefits of confirming our diagnosis.

To cite: Chan C, Roberts JM. *BMJ Case Rep* Published Online First: [*please include* Day Month Year]. doi:10.1136/bcr-2017-221580

Table 1 Relevant cortisol and UFC levels

	Morning cortisol (normal 120–160 nmol/L)	Morning cortisol after dexamethasone challenge (nmol/L) (normal 120–160 nmol/L)	UFC (normal 8–119 nmol/day)
Initial	3319	3698	~16 000
Respiratory failure, on metyrapone	1389		
Pre-MWA, on metyrapone	427		
Post-MWA, off metyrapone	774		
2 weeks post-MWA	334	108	228

MWA, microwave ablation; UFC, urinary free cortisol.

TREATMENT

While awaiting bilateral surgical adrenalectomy, the patient's hypertension was initially controlled with amlodipine 10 mg daily, candesartan 32 mg daily and spironolactone 75 mg twice a day. She required 60 meQ of potassium chloride four times a day to maintain normal potassium levels. She was started on ketoconazole 100 mg three times day, but this was replaced with metyrapone due to ketoconazole-induced hepatic injury. Four days into metyrapone therapy and 2 days before she was scheduled for adrenalectomy, she developed hypoxaemic respiratory failure secondary to acute respiratory distress syndrome requiring emergent intubation. While in the ICU, she was diagnosed with cytomegalovirus (CMV) pneumonitis and *Pneumocystis jirovecii* pneumonia (PJP), both confirmed by PCR. She was treated for several additional infections including *Staphylococcus aureus* bacteraemia, *Citrobacter* pneumonia and multiple urinary tract infections. Her intensive care unit (ICU) stay was further complicated by rapid atrial fibrillation, acute kidney injury requiring dialysis, prolonged ventilator wean requiring tracheostomy and significant deconditioning. Her morning cortisol was maintained between 400 and 700 nmol/L on metyrapone, although with significant side effects including headache and diarrhoea. When she returned to the ward after 1 month, she was too frail for surgical adrenalectomy.

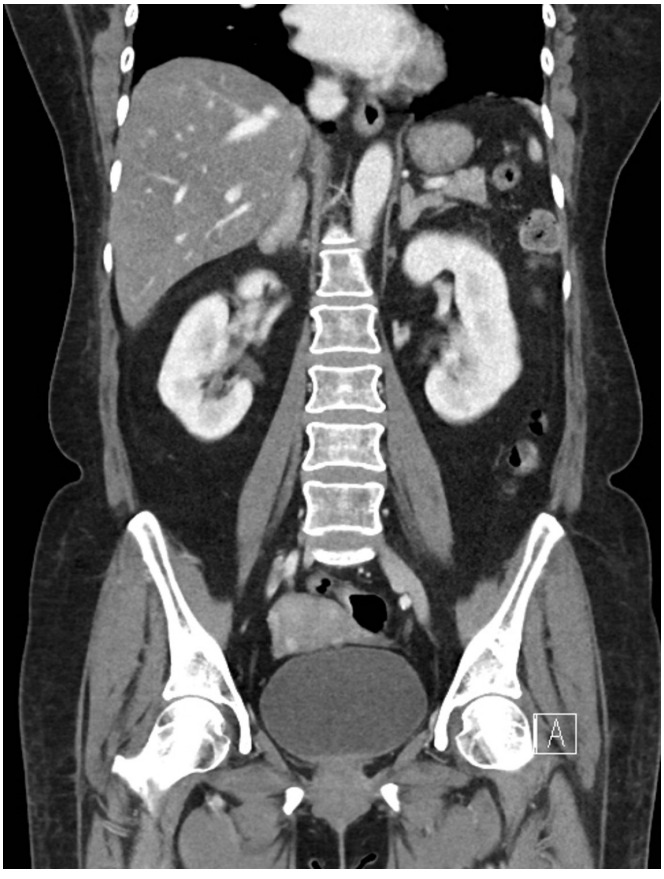

Figure 1 Abdominal CT reveals marked bilateral adrenal hyperplasia but no adrenal tumour.

The patient then underwent CT-guided bilateral microwave ablation (MWA) of the adrenal glands as a bridge to surgery. Ablation was performed at 65 W for 1 min, followed by 45 W for 6 min. While on metyrapone, her blood pressure had been maintained on amlodipine 5 mg daily and metoprolol 12.5 mg twice a day prior to the procedure, but during the procedure, she experienced a hypertensive crisis, requiring intravenous esmolol 40 mg and labetalol 20 mg in total. Her morning cortisol the day following the procedure, off metyrapone, was 774 nmol/L and decreased to 334 nmol/L 2 weeks later (table 1). Following a 1 mg dexamethasone suppression test, morning cortisol was appropriately suppressed at 108 nmol/L. UFC remained mildly elevated at 228 nmol/day. The patient experienced significant symptomatic improvement following the procedure.

OUTCOME AND FOLLOW-UP

The patient's functional status had improved significantly by 2 weeks after the ablation. Whereas she was essentially bedbound after her ICU stay, after intense physiotherapy, she was able to ambulate short distances with a two-wheeled walker and was able to have short excursions outside the hospital with her family. Consideration was thus made regarding definitive adrenalectomy, repeat ablation or restarting metyrapone. Unfortunately, adrenalectomy required an open operation due to postablation distortion of anatomy and destruction of tissue planes, making a laparoscopic approach difficult in the immediate postablation time period. Similarly, repeat ablation would risk damaging adjacent tissues as the remaining adrenal tissue was close to visceral organs.

Given her significant improvement from a laboratory and clinical standpoint, her relative deconditioning and technical difficulties of operative or percutaneous procedures, the patient did not undergo any further intervention. She was discharged to a rehabilitation facility off all steroidogenesis inhibitors, potassium supplementation and antihypertensive medications. She had follow-up with endocrinology with monthly dexamethasone suppression testing. Further screening for her primary tumour was felt to be unnecessary.

Six months after her discharge, the patient returned to the hospital for bilateral laparoscopic adrenalectomy. Notably, there was significant fibrosis around both adrenal glands due to previous ablation. Dissection around the right adrenal gland resulted in a small tear to the lateral edge of the liver, easily controlled intraoperatively, and dissection around the left adrenal gland came close to the body of the pancreas requiring a drain to be left in situ for 2 days. She suffered no significant complications and was discharged 2 days later. Her morning cortisol levels have remained appropriately suppressed following dexamethasone challenge.

DISCUSSION

Our case is notable for two reasons—first, the combination of PJP and CMV pneumonitis in Cushing's syndrome has only been reported in one case report in the past.[4] Second, MWA for occult ectopic ACTH syndrome has also only been described once.[5]

The incidence of opportunistic infections in Cushing's syndrome is approximately 11%–17%.[6] Hypercortisolaemia induces lymphopaenia, cellular immune deficiency, and reduced number and function of CD4 cells. It also results also in inhibition of nuclear factor-kappa B, interfering with the production of cytokines that play an integral role in the immune response to bacterial infections.[7] The degree of hypercortisolaemia in ectopic ACTH-related Cushing's syndrome is far higher than that in pituitary-dependent Cushing's disease and thus increases the extent of immunological impairment and risk of infection.[8 9] Cortisol levels in pituitary Cushing's disease rarely exceed 1000 nmol/L, whereas most opportunistic infections will present above this level.[10] The most common opportunistic pathogens are *P. jirovecii*, *Cryptococcus neoformans*, *Aspergillus fumigatus* and *Nocardia asteroides*.[9 10]

The symptoms of PJP are usually unmasked after treatment for Cushing's syndrome has been initiated, when the anti-inflammatory effects of hypercortisolaemia have been attenuated.[6] Graham and Tucker found that in patients with Cushing's syndrome complicated by PJP, serum cortisol levels measured above 3342 nmol/L.[9] In another case series by Bakker *et al*, serum cortisol levels were consistently above 2759 nmol/L.[10] Bakker *et al* have thus suggested PJP prophylaxis for patients with serum cortisol over 2500 nmol/L.[10] In their 2015 clinical practice guideline, the Endocrine Society suggests PJP prophylaxis for UFC greater than five times normal.[11]

While PJP is a common opportunistic pathogen in Cushing's syndrome, CMV infection is rarely reported. In a review of the literature, we found five cases of CMV infection in association with Cushing's syndrome and only two cases of CMV pneumonitis; the other three cases involved the gastrointestinal tract.[4 12–15] Sieber *et al* report a case of concomitant PJP, CMV pneumonitis and disseminated aspergillosis in the setting of an ACTH-producing small cell carcinoma.[4] The patient died of respiratory failure following an open lung biopsy. Goto *et al* report a case of Cushing's syndrome secondary to diffuse large B-cell lymphoma with adrenal involvement, complicated by acute respiratory distress syndrome from *Cryptococcus* and CMV coinfection.[12] The patient died of respiratory failure soon after metyrapone was initiated. Morning cortisol levels were remarkably elevated at 3200 nmol/L and 2061 nmol/L, respectively. Both patients died before adrenalectomy could be performed (on postadmission day 6 and day 11, respectively). Our case therefore represents the first reported case of CMV pneumonitis in a patient with an occult ACTH-secreting tumour and the first patient who has survived.

Our patient displayed remarkable hypercortisolaemia with UFC over 100 times normal. It is difficult to determine whether initiation of PJP or CMV prophylaxis at the time of diagnosis would have prevented her respiratory failure and subsequent prolonged ICU stay. Nevertheless, our case highlights the importance of careful monitoring for opportunistic infections when initiating treatment in patients with ectopic ACTH syndrome, especially those with marked hypercortisolaemia. We suggest PJP prophylaxis for patients with serum cortisol over 2500 nmol/L. In a stable patient, consideration should be made to screen for common opportunistic pathogens including the aforementioned PJP, *Cryptococcus*, *Aspergillus* and *Nocardia*, but additionally hepatitis B, hepatitis C, *Mycobacterium tuberculosis* and *Mycobacterium avium* complex, and initiate prophylactic treatment if positive. This should be done prior to initiation of adrenal enzyme inhibitors in patients with extreme hypercortisolaemia (eg, morning cortisol >2000 nmol/L) to avoid the possibly life-threatening effects of immune reconstitution in patients with unmasked infections, similar to the phenomenon of immune reconstitution inflammatory syndrome seen in patients with HIV, who have analogous defects in cellular immunity.[16]

The second notable aspect of our case is the method of cortisol reduction. The gold standard treatment for ectopic ACTH syndrome is surgical resection, although this is not always possible, for example in metastatic disease or occult tumours, as was our case.[2] In cases where the primary ACTH-secreting tumour is not found, morbidity and mortality is usually secondary to hypercortisolaemia as opposed to the primary malignancy, and the prognosis is generally favourable if the hypercortisolaemia is corrected.[17] First-line medical therapy consists of adrenocortical steroidogenesis inhibitors, most commonly ketoconazole or metyrapone. Two other options are mitotane, which has a slower onset of action, and etomidate, which is a parenteral option for rapid lowering of cortisol in emergency settings.[2] Bilateral adrenalectomy in additional to medical therapy has been shown to improve quality of life and decrease mortality related to Cushing's-related complications when compared with medical therapy alone.[18]

Our patient experienced an 18-day delay between initial consultation with urology and her scheduled adrenalectomy. In a retrospective review of 65 cases of Cushing's syndrome at a tertiary-care centre, three patients who experienced a delay in adrenalectomy suffered a series of Cushing's-related complications and thereafter were no longer candidates for adrenalectomy due to decreased functional status.[18] This highlights the importance of early surgical intervention in Cushing's disease, even in patients with high surgical risk.[11 18]

For patients who are unable to undergo surgery, percutaneous adrenal ablation has recently become a therapeutic option. Adrenal ablation has been used primarily for adrenal tumours; there are limited data on its use in treating non-neoplastic conditions such as adrenal hyperplasia resulting from ectopic Cushing's syndrome. Available methods include radiofrequency ablation, cryoablation, chemical ablation and MWA, each with their own advantages and risks. MWA has the advantage of a larger ablation volume, decreased procedural pain and shorter treatment duration.[19]

We have found one case report of MWA for treatment of an occult ectopic ACTH-producing tumour[5]; ours will be the second. There are two other cases of ectopic ACTH syndrome, secondary to medullary thyroid cancer and pancreatic neuroendocrine tumour, respectively, that have been treated with MWA.[5 20] All four cases were complicated by intraoperative hypertensive crisis secondary to catecholamine release from adrenal tissue. Direct-acting vasodilators and short-acting adrenergic antagonists should be available to counteract the effects of excessive catecholamine release including tachycardia and hypertension. Preprocedural administration of adrenergic antagonists is usually recommended.[5 19 20] Two other cases of percutaneous ablation for adrenal hyperplasia have also been reported, using alcohol ablation by retrograde adrenal vein.[21 22]

In our case, consideration was made towards a second ablation or proceeding to laparoscopic adrenalectomy; however, both these options were deferred due to increased risk of injury to surrounding tissues following MWA. The fact that MWA may limit future therapeutic options was not recognised prior

to the procedure. In future cases, consideration must be made regarding the timing and method of intervention—that is, if a patient is stable on medical treatment and it is likely that he or she will be able to withstand adrenalectomy within a reasonable time course, percutaneous ablation should not be performed.

The three previously reported patients required glucocorticoid supplementation after MWA rendered them Addisonian. Our patient is unique in that postprocedure cortisol levels did not reach subnormal levels and she therefore did not require replacement therapy. This calls into the question the role of partial ablation of the adrenal glands, analogous to partial adrenalectomy, which is recommended for certain adrenal tumours to preserve cortical function and avoid lifelong steroid replacement.[23] Certainly, more research is needed in the area before partial ablation can be recommended.

Our experience demonstrates that percutaneous ablation is a viable alternative in patients with ectopic ACTH syndrome in whom medical therapy has failed and surgical adrenalectomy is not feasible. Further research comparing the efficacy and complication rates between percutaneous ablation and surgical adrenalectomy is needed. As well, research is needed to determine the optimal method of percutaneous intervention.

Learning points

- The degree of hypercortisolaemia in ectopic adrenocorticotropic hormone syndrome is greater than that in Cushing's disease.
- Screen for opportunistic infections including *Pneumocystis jirovecii*, *Cryptococcus*, *Aspergillus*, *Nocardia*, hepatitis B and C, tuberculosis and *Mycobacterium avium* complex in patients with serum cortisol >2000 nmol/L prior to initiating adrenal-directed therapy.
- Microwave ablation of the adrenal glands is a feasible alternative in patients with Cushing's syndrome who are not candidates for surgery.
- Percutaneous ablation may make subsequent laparoscopic adrenalectomy technically difficult.

Acknowledgements The authors would like to acknowledge Dr. Ravjot Dhatt for radiological consultation and Dr. Joseph Leung for endocrinology input.

Contributors CC was the primary author in this manuscript. She is a resident who was involved in the patient's care. She consented the patient for case report publication, wrote up the case, and performed a literature review and analysis. JMR is an internal medicine attending who was involved in the patient's care. He provided guidance in writing the report and was involved in the editing process.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Lacroix A, Feelders RA, Stratakis CA, *et al*. Cushing's syndrome. *Lancet* 2015;386:913–27.
2 Biller BM, Grossman AB, Stewart PM, *et al*. Treatment of adrenocorticotropin-dependent Cushing's syndrome: a consensus statement. *J Clin Endocrinol Metab* 2008;93:2454–62.
3 Dekkers OM, Horváth-Puhó E, Jørgensen JO, *et al*. Multisystem morbidity and mortality in Cushing's syndrome: a cohort study. *J Clin Endocrinol Metab* 2013;98:2277–84.
4 Sieber SC, Dandurand R, Gelfman N, *et al*. Three opportunistic infections associated with ectopic corticotropin syndrome. *Arch Intern Med* 1989;149:2589–91.
5 Sarma A, Shyn PB, Vivian MA, *et al*. Single-session CT-guided percutaneous microwave ablation of bilateral adrenal gland hyperplasia due to ectopic ACTH syndrome. *Cardiovasc Intervent Radiol* 2015;38:1335–8.
6 Keenan N, Dhillo W, Williams G, *et al*. Unexpected shortness of breath in a patient with Cushing's syndrome. *Lancet* 2006;101:334–8.
7 Ntali G, Grossman A, Karavitaki N. Clinical and biochemical manifestations of Cushing's. *Pituitary* 2015;18:181–7.
8 Sarlis NJ, Chanock SJ, Nieman LK. Cortisolemic indices predict severe infections in Cushing syndrome due to ectopic production of adrenocorticotropin. *J Clin Endocrinol Metab* 2000;85:42–7.
9 Graham BS, Tucker WS. Opportunistic infections in endogenous Cushing's syndrome. *Ann Intern Med* 1984;101:334–8.
10 Bakker RC, Gallas PR, Romijn JA, *et al*. Cushing's syndrome complicated by multiple opportunistic infections. *J Endocrinol Invest* 1998;21:329–33.
11 Nieman LK, Biller BM, Findling JW, *et al*. Treatment of cushing's syndrome: an endocrine society clinical practice guideline. *J Clin Endocrinol Metab* 2015;100:2807–31.
12 Goto T, Takata T, Sato E, *et al*. [A case of acute respiratory distress syndrome caused by cryptococcus and cytomegalovirus co-infection after Cushing's syndrome treatment]. *Kansenshogaku Zasshi* 2013;87:39–43.
13 Jain P, Rai RR, Udawat H, *et al*. Cytomegalovirus colitis in a patient with endogenous Cushing's syndrome. *Hung Med J* 2007;1:533–6.
14 Bhansali A, Dutta P, Bhat MH, *et al*. Unusual opportunistic infection associated with endogenous Cushing syndrome. *Endocrinologist* 2006;16:125–7.
15 Bami K, Chan W, Steen O, *et al*. An unusual cause of severe immunosuppression. *CGJIM* 2015;10:48–51.
16 Nelson AM, Manabe YC, Lucas SB. Immune reconstitution inflammatory syndrome (IRIS): what pathologists should know. *Semin Diagn Pathol* 2017;34:340–51.
17 Alexandraki KI, Grossman AB. The ectopic ACTH syndrome. *Rev Endocr Metab Disord* 2010;11:117–26.
18 Morris LF, Harris RS, Milton DR, *et al*. Impact and timing of bilateral adrenalectomy for refractory adrenocorticotropic hormone-dependent Cushing's syndrome. *Surgery* 2013;154:1174–84.
19 Venkatesan AM, Locklin J, Dupuy DE, *et al*. Percutaneous ablation of adrenal tumors. *Tech Vasc Interv Radiol* 2010;13:89–99.
20 Zener R, Zaleski A, Van Uum SH, *et al*. Successful percutaneous CT-guided microwave ablation of adrenal gland for ectopic Cushing syndrome. *Clin Imaging* 2017;42:93–5.
21 Gatti A, Baroni MG, Romeo S, *et al*. A case of severe occult ectopic adrenocorticotropin syndrome treated with retrograde venous adrenal ablation using ethanol. *J Endocrinol Invest* 2008;31:1135–6.
22 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.
23 Nagaraja V, Eslick GD, Edirimanne S. Recurrence and functional outcomes of partial adrenalectomy: a systematic review and meta-analysis. *Int J Surg* 2015;16:7–13.