An Unusual Cause of Atrial Fibrillation

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James Shand grew up in Drury in South Auckland before studying medicine at the University of Auckland. After having an incredible experience in Whangarei as a 5th year, James decided to return for his first job. Having a work-life balance and sustaining his life outside of medicine is very important to James. Within medicine, his interests lie in General Medicine and sees himself following this path in the long term.

CASE REPORT

A 74 year old Maori woman presented to hospital following a collapse at her GP practice.

She had a three week history of increasing anxiety, global weakness and new palpitations. These were not associated with chest pain or shortness of breath. She saw her GP the morning of her admission and collapsed after the consultation.

She did not lose consciousness, had no seizure activity, palpitations or chest pain and attributed the fall to leg weakness.

She was hospitalised where an ECG showed atrial fibrillation, and serial troponins came back at 123 and 112 units mEq/L. Blood tests showed a serum potassium of 1.7 mEq/L (normal range 3.5-4.5). Urine potassium was not checked.

Her potassium level was normal when last measured in 2008.

Symptomatically, she continued to describe increased weakness, palpitations and anxiety, but denied muscle cramps. She did note that her skin appeared unusually tanned recently despite minimal sun exposure.

She was not on any new medications, took no steroids and had no vomiting or diarrhoea. Her weight was stable and there were no significant respiratory symptoms.

The most notable aspect of her past medical history was her 10 year history of hypertension which was well-controlled with diltiazem, doxazosin and a combination cilazapril/hydrochlorothiazide tablet which was stopped on admission. She had a mild chronic idiopathic thrombocytopenia, mild renal impairment and diet-controlled dyslipidaemia.

Aside from the previously mentioned antihypertensive medications, she was taking the over-the-counter medication "Res-V plus" (Resveratrol) and vitamin B tablets. She had no known allergies.

There was no family history of hypokalaemia and apart from an unspecified "thyroid problem" affecting one of her daughters, there was no family history of endocrine or autoimmune disease.

Notable positive findings on examination were increased pigmentation in the palmar creases and over the elbows, a 2/6 ejection systolic murmur loudest over the right upper sternal edge and global symmetrical 4+to 5 power with decreased reflexes throughout. She had no clinical findings of Cushing's, was not cachexic and her chest was clear.

Relevant blood results on admission were:

Blood Test	Value	Normal Range
Potassium (mEq/L)	1.7	3.5 - 4.5
Sodium (mEq/L)	145	135 - 145
VBG pH	7.62	7.32 - 7.42
VBG Base Excess (mEq/L)	16.4	-2.0 - 3.0
Blood Sugar Level (mmol/L)	9.3	3.5 - 7.7
Platelets ($x10^9$/L)	117	150 - 400
White Cell Count ($x10^9$/L)	15.1	4 - 11
Neutrophils ($x10^9$/L)	14.2	1.9 - 7.5

Further tests revealed a raised 8 AM cortisol of 3100 nmol/L (200-700) and a raised ACTH of 60 pmol/L (2-11).

In light of these results, a diagnosis of probable ACTH-dependent Cushing's syndrome was made. The patient had a negative high dose dexamethasone suppression test and this, combined with her markedly elevated ACTH levels, meant ectopic ACTH production was most likely.

Chest and abdominal CT scan revealed a large mass in her mediastinum with multiple metastases in her liver and spine. She proceeded to bronchoscopy and biopsy which revealed an invasive small cell lung cancer. She was referred to oncology and received one course of chemotherapy before passing away from neutropenic sepsis.

DISCUSSION

Cushing's syndrome is a relatively rare endocrine condition, having a global incidence of 0.7-2.4 people per million per year.[1] However, it is associated with a five-fold increase in mortality if untreated and, as such, requires prompt recognition and appropriate management.[1]

The disease itself is marked by "extended exposure to excessive glucocorticoids from endogenous or exogenous sources".[2] Exogenous (iatrogenic) administration is a much more common cause of Cushing's syndrome than endogenous excess, though such cases are usually identifiable from the history.[3]

Endogenous cortisol excess, on the other hand, is a disease state which may arise due to derangement at any point along the hypothalamic-pituitary-adrenal axis. Around 80 % of cases of endogenous hypercortisolism are due to ACTH-secreting pituitary adenomas, manifesting as the so-called Cushing's disease.[4]The remaining cases are largely due to adrenal hyper-secretion of cortisol by an autonomous adenoma with around 5% attributable to ectopic ACTH-secreting tumours and a small number from other causes such as CRH-secreting tumours[4]

Ectopic ACTH secretion is associated with a variety of solid tumours, most

of which are neuroendocrine in origin.[5] Amongst these tumours, the vast majority are thoracic, with bronchial carcinoid tumours being the largest group.[5]

Hypokalaemia is a relatively uncommon feature in Cushing's syndrome, with a reported prevalence of 10%.[6] Interestingly, this rate is much higher amongst the subgroup of patients with ectopic ACTH secretion. A 2002 study found the rate of hypokalaemia within these patients to be 57%, with the incidence of hypokalaemia being directly related to the urinary cortisol level but not the serum ACTH level.[6]

In normal physiology, serum potassium is regulated by the actions of the mineralocorticoid aldosterone on the proximal tubule of the kidney. Aldosterone is released by the adrenal glands and acts on the Na+/K+ exchanger in the distal renal tubules to increase sodium reabsorption and potassium secretion.[7]

The mechanism behind the hypokalaemia of Cushing's syndrome is incompletely understood but is thought to be related to the saturation of the enzyme 11-B hydroxysteroid dehydrogenase (11-BHSD2) which is expressed in exceptionally high concentrations by renal tubule cells.[7] This enzyme is responsible for the local conversion of circulating cortisol into its 11-oxo form, cortisone.[6]

Cortisol actually has an in vitro mineralocorticoid effect comparable to that of aldosterone. However, when cortisol is catalysed to cortisone, it loses its ability to bind to the mineralocorticoid receptor and hence its mineralocorticoid action. This explains why, even though cortisol is present in the circulation at levels up to 1000 times those of aldosterone, it is the latter that is, in vivo, the most important regulator of electrolyte balance.[6]

In Cushing's syndrome, it is hypothesised that the high circulating cortisol levels saturate 11-BHSD2, meaning large amounts of active cortisol are no longer converted to inactive cortisone. This results in increased cortisol levels within the kidney which leads to increased mineralocorticoid receptor occupancy and subsequent hypokalaemia via up-regulation of the sodium-potassium exchanger.[6]

This hypothesis is supported by the clinical findings of children who are born with a congenital absence of 11-BHSD2. An exceptionally rare mutation, these patients exist in a state of apparent mineralocorticoid excess, with marked hypertension and hypokalaemia.[8]

Further evidence for the 11-BHSD2 hypothesis comes from observational data regarding patients who consume huge quantities of certain types of liquorice. It has long been recognised that such patients can present with hypokalaemia and hypertension and this is now attributed to the actions of one ingredient, glycyrrhizic acid. This substance has been demonstrated in vitro to inhibit the action of 11-BHSD2 and it is currently assumed that this is the mechanism behind the clinical presentation of these patients.[8]

These data, combined with the correlation between cortisol levels and hypokalaemia, point towards 11-BHSD2 saturation as a likely mechanism for hypokalaemia in Cushing's syndrome. However, they do not explain the observation of a higher prevalence among those who have ectopic ACTH compared with other forms of hypercortisolism.

The mechanism behind this observed difference remains somewhat elusive. It has been demonstrated that ACTH has no in vitro inhibitory effect on 11-BHSD2 and there is no direct correlation between ACTH levels and the presence or severity of hypokalaemia.[6] Beside a direct effect of ACTH, other proposed mechanisms have included actions of co-secreted molecules or the effects of the comparatively high levels of serum cortisol seen in this setting.[9] However, none of these theories have been conclusively proven and the jury is still very much out on the pathophysiological mechanism behind this observation.[9]

In conclusion, this patient's presentation, with atrial fibrillation and weakness, was secondary to an occult aggressive lung cancer resulting in the paraneoplastic phenomenon of ectopic ACTH syndrome. Molecular interactions within body systems explain her presentation and are a reminder of the complex mechanisms at play within the human body. Although there is still some way to go to explain all features of ectopic ACTH secretion, research to date has given us an insight into this disease state and will hopefully continue to shed light on this uncommon but important condition.

REFERENCES

1. Newell-Price J., Bertagna X., Grossman A. & Nieman K. (2006).
Cushing's syndrome.
The Lancet, 367, 1605-1617.0

2. Arnaldi G, Angeli A, Atkinson AB, Bertagna X, Cavagnini F, Chrousos GP, Fava GA, Findling JW, Gaillard RC, Grossman AB, Kola B, Lacroix A, Mancini T, Mantero F, Newell-Price J, Nieman LK, Sonino N, Vance ML, Giustina A & Boscaro M. (2008).
Diagnosis and complications of Cushing's syndrome: a consensus statement.
Journal of Clinical Endocrinology and Metabolism, 88 (12), 5593-602.

3. Makras P., Toloumis G., Papadogias D., Kaltsas G. & Besser M. (2006).
The diagnosis and different diagnosis of endogenous Cushing's syndrome.
Hormones, 5(4), 231-250.

4. Gualraldi F. & Slavatori R., (2012).
Cushing Syndrome: Maybe not so uncommon of an endocrine disease.
Journal of the American board of family medicine, 25(2), 199-208.

5. Isidori, A. & Lenzi, A. (2007).
Ectopic ACTH syndrome.
Arquivos Brasileiros de Endocrinologia & Metabologia,51(8), 1217-1225

6. 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.
Annals of the New York academy of science, 970, 134-144.

7. Funder, J. (2010).
Minireview: Aldosterone and mineralocorticoid receptors: past, present and future.
Endocrinology, 151 (11), 5098-5102.

8. Benediktsson R. & Edwards CR. (1994).
Apparent mineralocorticoid excess.
Journal of Human Hypertension 8(5), 371-5.

9. Longo D., Fauci A., Kasper D., Hauser S., Jameson L. & Loscalzo J. (2011).
Harrison's Principles of Internal Medicine 18e. New York: McGraw-Hill Professional.