CASE REPORT

A Case Report on Biochemical Aberrations in Disseminated Histoplasmosis: The Clues Toward Addison's Disease

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ABSTRACT

The incidence of Addison's disease (AD) is rare. One of the most common causes of AD in developed countries is autoimmune. On the other hand, in developing countries, infective causes still predominate. The symptoms are mostly insidious in onset and non-specific, making it challenging to diagnose AD. The delay in starting the right treatment predisposes to high mortality due to Addison's crisis. Hence, biochemical parameters play a vital role in diagnosing AD since they usually will present with prominent hyponatraemia, hyperkalaemia and hypoglycaemia. Here, we report a case of a 66-year-old man with multiple co-morbidities and disseminated histoplasmosis who presented with asymptomatic hyponatraemia and hyperkalaemia and was eventually diagnosed with Addison's disease. Although the non-specific symptoms from his multiple co-morbidities obscured the diagnosis of AD, comprehensive biochemical tests have helped in establishing the diagnosis.

Keywords: Hyponatraemia, Hyperkalaemia, Addison's disease, Disseminated histoplasmosis, Short synacthen test

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INTRODUCTION

Addison's disease (AD) is rare with reported cases accounting for about 120 per million population in the West (1). Tuberculosis is still the most frequent aetiology of AD in developing countries, followed by histoplasmosis (1).

Diagnosing hypoadrenalism in chronic illness can be tough because of the vague symptoms. However, the symptoms, together with the deranged biochemical parameters, can give clues in the diagnosis and could be used as a predictor of the occurrence of its catastrophic complication, Addison's crisis. Biochemical aberrations in AD may include hyponatraemia, hyperkalaemia and mild non-anion gap metabolic acidosis occurring mainly due to insufficient mineralocorticoid and glucocorticoid secretion (2).

We report a case of a man who developed stage 5 chronic kidney disease (CKD) secondary to disseminated histoplasmosis (DH). On the subsequent visit, he was found to have refractory hyperkalaemia and was later diagnosed with AD.

CASE REPORT

A 66-year-old gentleman was referred by the health clinic for abrupt worsening of estimated glomerular function (eGFR) from 69 to 20 mL/min/1.73 m2 within a one-year duration in November 2018. He had a background history of dyslipidaemia, essential hypertension and hypothyroid post-radioactive iodine ablation for Graves' disease. Co-incidentally, bilateral adrenomegaly was found on magnetic resonance imaging. Therefore, renal and adrenal biopsies were undertaken. The biopsies' report showed Histoplasma sp. in the background of chronic granulomatous infection. He was then diagnosed with stage 5 CKD secondary to DH, completed intravenous amphotericin B for two weeks, and was discharged home with oral itraconazole and lifelong dialysis.

On his subsequent multidisciplinary clinic follow up, it was noted that he had fluctuating levels of potassium ranging from 5.4 mmol/L to 7.9 mmol/L (Table I), otherwise asymptomatic. During an elective admission for computed tomography (CT) of the thorax as part of DH surveillance, the laboratorian noted a potassium result of 7.3 mmol/L and promptly alerted the treating physician. Further history revealed that he had been experiencing mild lassitude. There was no history of recent weight loss since he was diagnosed with DH nor any recent travelling or outdoor activities. He had no complaints of

abdominal pain or other gastrointestinal symptoms. He denied taking any supplementary medicine and was not on any potassium-rich diet.

At this current presentation, his vital signs were stable with blood pressure ranging from 110 to 150/60 to 90 mmHg with no documented postural hypotension. Clinical examination was unremarkable, and an electrocardiogram showed normal sinus rhythm with a peaked T wave without any acute ischaemic pattern. The initial routine biochemical tests reported low normal serum sodium, a high normal adjusted calcium, hypomagnesaemia, hyperphosphataemia and a renal profile consistent with stage 5 CKD without acute deterioration from his baseline serum urea and creatinine (Table I). His blood gas analysis also showed mild normal anion gap metabolic acidosis (Table II).

Initially, hyperkalaemia was treated secondary to CKD. Lytic cocktails, regular six-hourly salbutamol nebulisers, and oral kalimate were administrated. Despite vigorous treatment, hyperkalaemia remained refractory. During day three of admission, a serum cortisol level measured late on the previous day was reported low about <28 nmol/L (Table I). Thus, intravenous hydrocortisone was initiated, causing prompt normalisation of the hyperkalaemia (Table I). A short synacthen test (SST) was done on day six of admission to determine the diagnosis of AD, and intravenous hydrocortisone was withheld overnight before the test. Unsurprisingly, the results showed a blunted response of cortisol level with marked adrenocorticotrophin hormone (ACTH) elevation (Table III), consistent with primary adrenal failure.

Taking into consideration the history, the pattern of biochemical aberrations and response to hydrocortisone, the diagnosis was revised to AD secondary to DH. After one week of hospital stay, he was discharged home well with oral hydrocortisone.

Table II: Blood Gas Analysis

	21/12/2018 Day 3 admission	23/12/2018 Day 5 admission	Reference range
pH	7.248	7.389	7.35 – 7.45
pCO_2	30.6	34	35.0 – 45.0 mmHg
HCO_3	14.1	21.2	22.0- 26.0 mmol/L
Base excess	-12.9	-4.1	-3.0 - +3.0 mmol/L

Table IV: Short Synacthen Test (SST)

24/12/2018	0 minute	30 minutes	60 minutes	Interpretation
Serum cortisol	<28 nmol/L	<28 nmol/L	<28 nmol/L	Blunted response of cortisol level <500 nmol/L at both 30- and 60-minutes indicative of adrenal insufficiency
Serum ACTH	449.9 pg/mL	313.4 pg/mL	358.9 pg/mL	Patient has raised baseline level with plasma ACTH >2fold the upper limit of the reference range with loss of negative feedback is consistent with AD

DISCUSSION

Addison's disease (AD) was named after Sir Thomas Addison who initially described the condition that was associated with a constellation of symptoms comprising of generalised lassitude, weak heart and peculiar discolouration of the skin (1). In Western countries, autoimmune was the most frequent aetiology causing AD, followed by tuberculosis, fungal and retroviral infections (1). Worldwide, there have been multiple cases reported on AD secondary to DH (2,3). However, the exact prevalence remains unknown. In Malaysia, there has been only one reported case of AD secondary to DH infected from bird droppings (4). To the best of our knowledge, this current case is the second documented case of AD secondary to DH in Malaysia.

Table I: Biochemical Profile

	15/11/2018 Baseline / Previous hospital discharge	7/12/2018 Day 21 post discharge	13/12/2018 Day 26 post discharge	18/12/2018 Day 31 post discharge	19/12/2018 Day 1 admission	20/12/2018 Day 2 admission	20/12/2018 Day 2 admission	21/12/2018 Day 3 admission	22/12/2018 Day 4 admission	23/12/2018 Day 5 admission	26/12/2018 Day of Discharge	Reference range
Urea	22.6	18.4	23.0	22.8	22.2	22.7	20.3	21.0	21.0	20.7	23.2	3.2 – 7.4 mmol/L
Creatinine	467.2	425.6	441.0	450.9	443.1	458.2				438.1	430.2	63.6 – 110.5 µmol/L
Sodium	138	135	132	135	134	135	128	129	133	131	131	136 – 145 mmol/L
Potassium	5.4	6.2	7.9	7.3	7.3	6.4	5.9	6.5	4.6	3.8	4.1	3.5 – 5.1 mmol/L
Corrected calcium	2.3	2.45				2.59					2.34	2.14 – 2.58 mmol/L
Magnesium	0.73	0.68				0.61					0.64	0.66 – 1.07 mmol/L
Phosphate	1.16	1.97				1.61					1.24	0.74 – 1.52 mmol/L
Fasting blood sugar						8.76						3.89 – 5.83 mmol/L
AM cortisol						<28						101.2 – 535.7 nmol/L

Signs of AD are mainly because of a deficiency of the two hormones, the glucocorticoid and mineralocorticoid, which result in weight loss, orthostatic hypotension, and electrolyte imbalance. Hyponatraemia, hyperkalaemia and hypercalcaemia are the commonly encountered biochemical changes (5). Patients with AD may also present with a pathognomonic feature of hyperpigmentation of the areas exposed to friction, including the palmar crease, knuckles, buccal mucosa and recent scar, due to the raised ACTH and other pro-opiomelanocortin peptides (5).

This patient had many other co-morbidities, including essential hypertension, which may have masked the expected hypotension typically seen in a patient with AD. He had been losing weight before he was diagnosed with DH; thus, any recent loss of weight for the past one month had possibly gone unnoticed. The patient had also been recently diagnosed with stage 5 CKD and was on regular dialysis. Non-specific features like reduced appetite, loss of weight and fatigue can be seen in both AD and CKD. Hyponatraemia is also seen both in AD and CKD. These overlapping signs and symptoms had added to the perplexity of this case.

The adrenal cortex secretes mainly glucocorticoids, mineralocorticoids and sex hormones, of which the former two are major regulators for water and electrolyte balance (5). Destruction of the adrenal cortex by fungal infiltration results in insufficiency of the hormones released, leading to severe biochemical derangement (Table I). Aldosterone increases hydrogen and potassium secretion in the urine. Therefore, low levels of aldosterone will result in potassium retention and loss of sodium and water, as seen in this patient at the initial presentation.

Apart from that, glucocorticoid also plays a role in the maintenance of blood pressure by sensitising the arterioles to the action of noradrenaline (5). Hence, the combination of both mineralocorticoid and glucocorticoid deficiencies will result in the reduction of renal perfusion followed by a decrease in glomerular filtration rate, which may worsen renal function parameters and result in acute kidney injury (AKI). This condition, however, was not seen in this patient because he was on regular dialysis.

Low morning cortisol with a low cortisol level after stimulation tests are the established tests to diagnose AD (5). Hypocortisolism will also result in a lack of negative physiological feedback to the hypothalamus, thus explaining the elevated level of plasma ACTH. The gold standard for the diagnosis of AD is a corticotropin stimulation test or also known as the SST, which was validated against the insulin tolerance test for diagnostic accuracy (5).

With regards to this case, the key to the diagnosis of AD was the presence of refractory hyperkalaemia despite multiple treatments. The low morning cortisol with the reversal of refractory hyperkalaemia upon administration of hydrocortisone further supported the diagnosis. The confirmatory test, which showed low baseline cortisol, a blunted response to synthetic corticotrophin and raised ACTH were coherent with the failing adrenal and loss of negative feedback inhibition to the hypothalamus.

CONCLUSION

In summary, although non-specific symptoms and multiple co-morbidities might have directed to the initial diagnosis of hyperkalaemia secondary to CKD, the presence of a classical pattern of the abnormal laboratory results and a high index of suspicion are essential in establishing an early diagnosis of AD despite its rarity. Studies on the prevalence of AD caused by a fungal infection in the local population will help in creating the awareness of the disease occurrence.

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REFERENCES

1. Brooke, A. & Monson, J. Addison's disease. Medicine. 2017;1–5.
2. Goswami, P., Dihingia, P., Dutta, A., Nath, R. & Das, S. Adrenal Histoplasmosis Not So Rare? - A Case Report with Review of Literature. Journal of Dental and Medical Sciences. 2016;15(6): 37–39.
3. Muhammed, H., Nampoothiri, R., Gaspar, B. & Jain, S. Infectious causes of Addison' s disease: 1 organ — 2 organisms! BMJ Case Rep. 2018; 1–3.
4. Shiun, A., Shiun, A. & Chang, H. Histoplasmosis with Addisonian Crisis: Call for Bird Control. Med J Malaysia. 2015;70(2): 104–105.
5. Bornstein S(Chair), Allolio B, Arlt W, Barthel A, Don-Wauchope A, Hammer G, et al. 2016. Diagnosis and Treatment of Primary Adrenal Insufficiency: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2016; 101: 1–26.