CASE REPORT

Hypokalaemic metabolic alkalosis, hypertension and diabetes: what is the link

Marius Vögelin,¹ Richard Cathomas,² Niklaus Kamber,³ Thomas Fehr¹¹Department of Internal Medicine, Kantonsspital Graubünden, Chur, Switzerland²Department of Internal Medicine, Division of Oncology, Kantonsspital Graubünden, Chur, Switzerland³Department of Internal Medicine, Division of Endocrinology, Kantonsspital Graubünden, Chur, Switzerland**Correspondence to** Professor Thomas Fehr, Thomas.fehr@ksgr.ch

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SUMMARY

Two years after diagnosis of a metastatic neuroendocrine gastrin-secreting tumour and after several cycles of chemotherapy and peptide receptor radionuclide therapy, a 56-year-old woman presented with hypokalaemic metabolic alkalosis, hypertension, leg oedema and new-onset diabetes mellitus. Further investigations revealed renal potassium loss confirmed by a transtubular potassium gradient of 16, fully suppressed serum aldosterone, but instead highly elevated blood levels of morning cortisol and adrenocorticotrophic hormone as well as increased urinary excretion of glucocorticoid and mineralocorticoid metabolites. Ruling out other causes, paraneoplastic hypercortisolism was diagnosed. Pharmacological inhibition of the steroid 11 β -hydroxylase with metyrapone resulted in complete resolution of metabolic alkalosis, hypokalaemia, hypertension, hyperglycaemia and leg oedema within 1 week.

BACKGROUND

The triad of hypokalaemia, metabolic alkalosis and hypertension is highly suspicious for mineralocorticoid excess and demands further evaluation. As the differential diagnosis is broad, further diagnostics should be chosen according to the patient's individual clinical presentation. The initial workup should include measurement of the aldosterone to renin ratio and the transtubular potassium gradient. Measurement of urinary cortisol metabolites detects excessive production of clinically active metabolites not captured by routine serum cortisol tests.

In patients with cancer with new-onset diabetes mellitus in addition to signs of mineralocorticoid excess, paraneoplastic hypercortisolism should be considered. Symptoms can occur late in the course of disease, as tumour progression and therapy may lead to selection of new tumour cell clones.

CASE PRESENTATION

At the age of 56 years, the patient was diagnosed with a neuroendocrine pancreatic tumour with gastrin-secreting hepatic metastasis. The latter manifested as an ulcerative pangastritis and duodenitis due to inappropriate gastrin secretion by neuroendocrine tumour cells, a clinical picture also known as 'Zollinger-Ellison syndrome'. Diagnosis was histologically confirmed by biopsies of the liver lesions (figures 1 and 2) and therapy was initiated by three cycles of peptide receptor radionuclide therapy (PRRT). Afterwards, the somatostatin analogue octreotide was administered as

maintenance treatment to inhibit gastrin secretion of neuroendocrine cells.¹ Eighteen months after initial diagnosis, substantial progression of the liver metastases was noted, and a second biopsy showed similar histological and immunohistochemical characteristics with high expression of somatostatin receptor 2 and persistently elevated proliferation index (Ki67 50%) (figure 1, Inset). Palliative chemotherapy with carboplatin and etoposide was administered for six cycles without adequate response. For this reason, the patient proceeded to receive further two cycles of PRRT.

Shortly after her last PRRT cycle and 2 years after initial diagnosis, the patient presented with hyperosmolar, hyperglycaemic crisis, metabolic alkalosis, hypokalaemia and hypertension. Laboratory results are shown in table 1. Furthermore, massive pitting oedema of both lower limbs was noted. These developed over the past 5 months together with general weakness, polyuria and polydipsia. Initial treatment included substitution of crystalloids and potassium, intensified insulin therapy and antihypertensive medication.

As hypertension in combination with water retention and glucose intolerance is suspicious of Cushing's syndrome and the triad with hypokalaemia, metabolic alkalosis and hypertension is characteristic for hyperaldosteronism, the synopsis of all these findings pointed towards a common cause. After restoring euglycaemia, further workup revealed renal potassium loss as shown by a transtubular potassium gradient of 16. In the renin-aldosterone test, serum aldosterone was fully suppressed and renin activity within normal range, ruling out primary hyperaldosteronism. Instead, blood levels of morning cortisol were elevated to a threefold and adrenocorticotrophic hormone (ACTH) to a sixfold of the upper standard value. Furthermore, a steroid profile of the urine showed marked overproduction of both glucocorticoid and mineralocorticoid metabolites. A serological test for corticotropin-releasing hormone (CRH) turned out negative. Consequently, autonomous secretion of ACTH was suspected. An MRI of the head and pituitary showed no pathological findings, and therefore, paraneoplastic production of ACTH was considered the most plausible explanation.

TREATMENT

Oral therapy with metyrapone 250 mg four times daily was initiated. This drug blocks cortisol synthesis by inhibiting steroid 11 β -hydroxylase.

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Figure 1 Liver biopsy showing metastasis of the neuroendocrine tumour. Inset: immunohistochemistry Ki-67 with proliferative index of about 50.

OUTCOME AND FOLLOW-UP

A short-term follow-up 8 days later revealed complete disappearance of hypertension, hypokalaemia and metabolic alkalosis. No more insulin was needed, and the marked leg oedema, which meanwhile reappeared despite initial therapy with diuretics, intravenous albumin and compression bandages, resolved permanently under administration of metyrapone.

Regular follow-up examinations showed no reappearance of diabetes, hypokalaemia, metabolic alkalosis or leg oedema while remaining on constant metyrapone treatment. The patient received further cytotoxic systemic treatment with good success, but eventually died 2 years later from progressive disease.

DISCUSSION

When both signs of glucocorticoid and mineralocorticoid excess are present, locating the underlying disorder more precisely on the hypothalamic–pituitary–adrenal axis has important therapeutic consequence. Concerning mineralocorticoid excess, measuring the aldosterone to renin ratio in a standardised setting

Figure 2 Biopsy of liver metastasis demonstrating gastrin production of the tumour cells by brown precipitates in the immunohistochemistry for gastrin.

Table 1 Laboratory results											
Date	5 April 2016	20 February 2016	8 December 2015	24 November 2015	18 September 2015	9 September 2015	11 August 2015	17 June 2015	30 May 2015	28 July 2014	17 September 2013
Serum creatinine (µmol/L)	55	56	47	116	35			55	63	52	52
Na+ (136–145 mmol/L)	138	139	137	143	140	142		141	143	139	143
K+ (3.4–4.5 mmol/L)	3.7	3.6	4.9	2.6	3.1	2.8	1.8	3.3	3.8	4.2	3.8
pH (7.25–7.45)	7.45	7.42	7.4	7.49	7.49	7.5					
Serum bicarbonate (22–26 mmol/L)	29	25	26	32	28	31					
Base Excess (−2.0–3.0 mmol/L)	5.4	0.8	2.5	8.6	3.8	8.2					
Glycated hemoglobin HbA1c (4.8%–5.9%)						10.5					
TTPG*						16					
Cortisol 8:00, serum (171–536 nmol/L)	2.73	258	366.5	1459							
ACTH (1.3–13.9 pmol/L)				86.3							
Aldosterone (pmol/L)					Not detectable†						
Renin (0.51–2.64 ng/mL/hour)					1.07†						

Laboratory results from September 2013 to April 2016. Metyrapone 4x250mg/day orally was started on 1 December 2015. Bold numbers show relevant values outside the normal range.
*TPG=translucidal potassium gradient (a quotient >2 in case of hypokalaemia indicates renal potassium loss).
†After volume challenge.
‡Before volume challenge.
ACTH, adrenocorticotrophic hormone.

Table 2 Differential diagnosis of hypokalaemic metabolic alkalosis and hypertension

Subgroup	Disorder	Aldosterone	Renin	ACTH
Acquired				
Hyperreninaemic	Renal artery stenosis	↑	↑	→
	Renin secreting tumour			
Hyporeninaemic	Aldosterone secreting adrenal adenoma/hyperplasia/carcinoma	↑	↓	→
'Pseudohyperaldosteronism'	Hypercortisolism of...			
	pituitary origin (ACTH)	↓	↓	↑
	Adrenal origin	↓	↓	↓
	Ectopic origin (CRH/ACTH/cortisol metabolites)	↓	↓	↓/→/↑
	Liquorice abuse (Acquired 11-β-hydroxysteroid dehydrogenase deficiency)	↓	↓	→
	Desoxycorticosterone producing tumour	↓	↓	↓/→
	Iatrogenic (medication)	↓	↓	↓
Genetic				
Hyporeninaemic	Glucocorticoid-remediable aldosteronism	↑	↓	→
'Pseudohyperaldo-steronism'	Liddle's syndrome	↓/→	↓	→
	Activating mineralocorticoid receptor mutation	↓	↓	↓/→
	Inherent 11-β-hydroxysteroid dehydrogenase deficiency	↓	↓	→
	Other enzyme deficiencies leading to accumulation of desoxycorticosterone	↓	↓	↓/→

ACTH, adrenocorticotrophic hormone; CRH, corticotropin-releasing hormone.

is very helpful to narrow down the list of differential diagnoses (table 2). Due to partial mineralocorticoid activity, both iatrogenic and endogenous excess of glucocorticoids can not only present in Cushing's syndrome, but also with signs of hyperaldosteronism. However, assuming a functioning negative feedback loop, in which physiological secretion of ACTH and CRH are both suppressed by circulating cortisol, the high levels of serum ACTH measured in our patient excluded an iatrogenic cause as well as primary hypercortisolism. Only autonomous secretion of ACTH or CRH by a neoplasm in the pituitary/hypothalamus or by ectopic paraneoplastic activity could therefore possibly explain all laboratory and clinical findings in our patient.

Concerning pituitary microadenomas not detectable in MRI, the commonly recommended test to distinguish between ectopic ACTH production and a corticotroph pituitary adenoma is a bilateral petrosal sinus sampling (BPSS) after administration of CRH.^{2,3} Alternatively, a high-dose dexamethasone trial (HDDT) that suppresses pituitary but not ectopic ACTH production can be used. In case of neuroendocrine tumours, HDDT has not a very high diagnostic accuracy. This is both due to difficulties defining a universal cut-off value and because some of these tumours do also respond to dexamethasone.^{4,5} In BPSS as well, several pitfalls and disadvantages must be considered. First, BPSS is an invasive and expensive procedure with potentially deleterious complications such as brain stem infarction. Furthermore, in case of ectopic CRH production, the diagnostic value of BPSS is substantially limited, as this condition may mimic Cushing's syndrome of pituitary origin. Several cases have been reported, in which simultaneous ectopic CRH and ACTH production has led to BPSS and HDDT results resembling pituitary Cushing's syndrome, sometimes even leading to unnecessary hypophysectomy.⁶⁻⁹ We, therefore, omitted both BPSS and HDDT, as its diagnostic benefit did not outweigh the risk and would not have substantially influenced the medical management in our patient.

Interestingly, ACTH immunostaining in biopsies of the liver metastases turned out negative in our patient. However, as these

biopsies were taken 6 months before appearance of mineralocorticoid excess, their diagnostic significance is questionable. We hypothesise that tumour cells could have gained new abilities or certain cell clones could have been selected by tumour therapy. As immunohistochemical tests for CRH are currently not available in Switzerland or other contacted laboratories in Europe and Japan, neither concomitant CRH production could be proven. A serological test for CRH turned out negative, but it has to be mentioned that this test is not widely used and its negative predictive value remains unknown. Eventually, we were able to diagnose autonomous production of ACTH, but could not directly prove that the neuroendocrine tumour cells are responsible. To do so, immunostaining for ACTH and CRH in new biopsies would be needed.

It is long known that also non-pituitary tumours can produce ACTH.¹⁰ Among them, tumours located in the lungs or gastrointestinal tract are the most common and characteristically present with Cushing's syndrome.^{11,12} However, reviewing current literature, only few cases with marked findings of mineralocorticoid excess due to paraneoplastic ACTH or CRH secretion are reported. Park *et al* described a 28-year-old woman diagnosed with a gastrin-secreting neuroendocrine tumour and ectopic ACTH and CRH production, also presenting with hypokalaemia, metabolic alkalosis and highly elevated cortisol and ACTH levels. Both ACTH and CRH were detected immunohistochemically in the biopsies of liver metastases. Mitotane was chosen for symptomatic therapy, resulting in marked decrease of both cortisol and ACTH levels.¹³ Shahani *et al* presented a similar case of ectopic CRH production in a patient with a neuroendocrine tumour of unknown primary and both signs of mineralocorticoid and glucocorticoid excess.¹⁴

By inhibiting the steroid 11β-hydroxylase, metyrapone reduces production of both glucocorticoids and mineralocorticoids. As the steroid 11β-hydroxylase is responsible for the last step in cortisol and second last step in aldosterone synthesis, metyrapone is effective in cases of excessive production of

CRH, ACTH or any metabolite before synthesis of deoxycorticosterone and 11-deoxycortisol. In our case, metyrapone effectively relieved symptoms and made comedication such as insulin, potassium supplementation and antihypertensive agents unnecessary. An alternative inhibitor of steroidogenesis is ketoconazole, which inhibits steroid synthesis on various levels in the adrenal cortex. Though, as it is feared for its potentially severe side effects (most notably its hepatotoxicity), it is not commonly used first line to treat cortisol excess.^{15 16} Further therapeutic options are surgical or medical adrenalectomy. The latter can be achieved by mitotane, as mentioned in the case of Park *et al.*¹³ Mitotane modifies cortisol production and is selectively cytotoxic in the adrenal gland. In comparison with metyrapone, however, the cytotoxic effect on the adrenal gland is irreversibly and side effects are common.^{17–19} We, therefore, favoured the option with metyrapone, which is known to be well tolerated.²⁰

Learning points

- Tumour patients often receive high dose of corticosteroids in the course of disease, which can result in iatrogenic Cushing's syndrome. Nevertheless, in patients with new-onset diabetes mellitus and signs of mineralocorticoid excess, paraneoplastic hypercortisolism needs to be considered. Symptoms can both precede tumour diagnosis or occur late in disease.^{4 21}
- When mineralocorticoid excess is suspected, initial diagnostics should include measurement of the aldosterone to renin ratio and the transtubular potassium gradient.
- Measurement of urinary cortisol metabolites may help detecting glucocorticoid or mineralocorticoid excess not captured by routine serum cortisol tests.
- Metyrapone can be a highly effective and well-tolerated symptomatic treatment in patients with paraneoplastic secretion of adrenocorticotrophic hormone.

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