

A rare cause of dysregulated metabolic syndrome: cortisol-producing adrenocortical carcinoma

L. Saes^{1*}, I.A. Boere¹, J. Hofland², M. Mulder³, R.A. Feelders²

¹Department of Medical Oncology, Erasmus MC Cancer Institute, Rotterdam, the Netherlands, Departments of ²Internal Medicine, sector Endocrinology, ³Internal Medicine, Erasmus MC, Rotterdam, the Netherlands, *corresponding author: email: l.saes@erasmusmc.nl

ABSTRACT

Adrenocortical carcinoma is a rare and highly malignant disease which can cause hypercortisolism leading to dysregulation of blood pressure and glucose levels. Most patients present with advanced disease. We describe the classic presentation of a functional adrenocortical carcinoma in a patient with metabolic syndrome.

KEYWORDS

Adrenocortical carcinoma, hypercortisolism, metabolic syndrome

CASE REPORT

A 75-year-old woman was referred to our hospital because of malignancy with liver metastases suspicious for hepatocellular carcinoma, as determined by CT scan and biopsy. She was known with type 2 diabetes since 2008, until recently well-regulated with dietary measures only. However, in the past months, she was admitted to the referring hospital twice because of congestive heart failure and hyperglycaemic deterioration with an HbA1c level of 116 mmol/mol, for which metformin and insulin glargine were started. She was taking several antihypertensive drugs (metoprolol, spironolactone, amlodipine and valsartan). Her symptoms at presentation included severe muscle weakness, leading to wheelchair dependency in one month. On clinical examination the patient appeared frail with proximal muscle weakness and haematomas localised at her right breast and arm after a recent collapse. Centripetal obesity and peripheral oedema were present. Blood pressure was 170/95 mmHg,

What was known on this topic?

Adrenocortical carcinomas (ACCs) are rare and frequently aggressive tumours that may be functional (hormone-secreting) and cause Cushing's syndrome and/or virilisation, or non-functional and present as an abdominal mass or as an incidental finding.

What does this add?

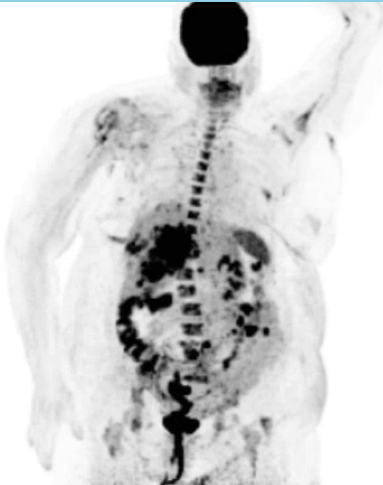
Since cortisol-producing ACC, and Cushing's syndrome in general, can mimic the dysregulation of more frequently seen chronic disorders as hypertension and diabetes, we want to remind clinicians that hypercortisolism might underlie this dysregulation.

pulse rate 86 bpm and her BMI was 34.3 kg/m². Laboratory testing showed: potassium 1.6 mmol/l (reference values 3.5-5.1), sodium 148 mmol/l (136-145), fasting glucose 14.6 mmol/l (4.0-6.1), phosphate 0.19 mmol/l (0.80-1.40), AST 109 U/l (< 31), LD 1381 U/l (< 247) and gamma-GT 964 U/l (< 38). A severe metabolic alkalosis was seen with a pH of 7.61 (7.35-7.45) and a bicarbonate of 47 mmol/l (21-27). Re-evaluation of the CT scan performed elsewhere identified a right-sided adrenal mass invading the right renal vein, inferior vena cava and right liver lobes (*figure 1*), suspicious for adrenocortical carcinoma (ACC) with liver metastases. Pulmonary embolisms were also detected. Additional hormonal testing yielded a serum cortisol level of 2180 nmol/ (200-800), a midnight salivary cortisol level of 339 nmol/l (< 2.8), elevated urinary cortisol excretion at 6232 nmol/24 hours (< 133) and a suppressed adrenocorticotrophic hormone (ACTH) concentration of 1.2 pmol/l (1-55). The serum steroid profile showed increased steroid precursor levels, including androstenedione, progesterone,

Figure 1. CT abdomen of the patient shows a right-sided adrenal mass, invading the right renal vein, inferior vena cava and right liver lobes, and liver metastases



Figure 2. FDG PET-CT shows greatly enhanced uptake in the right adrenal gland and liver metastases



17-hydroxyprogesterone, testosterone and oestradiol, while aldosterone levels were suppressed; 24-hour urinary excretion of (nor)metanephrines was not elevated. High uptake in the adrenal tumour and liver metastases was shown on the ^{18}F -fluoro-deoxyglucose positron emission tomography (FDG PET)-CT (figure 2). After revision by our pathologist, the liver biopsy was concordant with an ACC with positive Melan-A and synaptophysin staining and a Ki67 index of 20%. In summary, our patient was diagnosed with a stage IV ACC producing cortisol, androgen and oestrogen. Because of her poor performance status she was deemed ineligible for surgery, mitotane or intensive chemotherapeutic treatment. Cortisol excess was treated with metyrapone combined with hydrocortisone suppletion (block and replace therapy). Spironolactone

was increased from 50 mg once daily to 150 mg twice daily combined with potassium supplements to treat hypokalaemia. Three days after starting block and replace therapy a biochemical response was seen as evidenced by normalisation of the blood pressure, a lower insulin dose requirement and resolution of alkalosis. Treatment with low-molecular-weight heparin was started for pulmonary embolism. The patient was discharged to a palliative care facility.

DISCUSSION

ACCs are rarely seen with an incidence of 1-2 per million persons/year. Less than 5% of adrenal incidentalomas appear to be ACCs.¹ In adults, ACCs typically present in the fourth to fifth decade as a sporadic tumour, more often in women than in men (male female ratio 2:1). Approximately 60% of ACCs are functional causing a clinical syndrome as a result of an excess of cortisol, androgens, oestrogens or rarely aldosterone. ACTH-independent Cushing's syndrome caused by autonomous cortisol production is most frequently seen (45%) whereas less than 10% of patients present with virilisation alone.² The morbidity of Cushing's syndrome can be classified into metabolic, cardiovascular, musculoskeletal, infectious, reproductive, dermatological and neuropsychiatric manifestations.³ Glucose intolerance is primarily due to stimulation of gluconeogenesis by cortisol, direct suppression of insulin release and peripheral insulin resistance caused by progressive centripetal obesity.⁴ Direct stimulation of the mineralocorticoid receptor by glucocorticoid excess, exceeding the capacity of 11-beta-hydroxysteroid dehydrogenase type II in the kidney, causes hypertension, hypokalaemia and oedema.⁵ This pseudoaldosteronism was also present in our patient, also evidenced by the metabolic alkalosis. Thromboembolic events are frequently seen, caused by both increased plasma concentrations of clotting factors with activation of the coagulation cascade and inhibition of fibrinolysis.⁶ Due to clustering of cardiovascular risk factors, patients are at risk for cardiovascular events.⁷ Proximal muscle weakness and osteoporosis are caused by the catabolic effects of hypercortisolism on skeletal muscles and bone, respectively. An increased risk of infections is the result of immunosuppressive effects. An important clinical clue to the presence of hypercortisolism is the simultaneous development and increasing severity of several of the aforementioned symptoms causing considerable morbidity. Non-functional ACCs are often discovered as incidentalomas. When an ACC is suspected, hormonal evaluation should always be performed, including fasting blood glucose, serum potassium, cortisol, ACTH, 24-hour

urinary free cortisol, dexamethasone suppression test, aldosterone, renin, dehydroepiandrosterone-sulphate (DHEAS), androstenedione, testosterone, 17-hydroxyprogesterone and, on indication, oestradiol in men and postmenopausal women. It is also recommended to measure plasma or urinary (nor)metanephrines to exclude pheochromocytoma.¹ A CT scan can usually distinguish adenomas from ACCs; however, with magnetic resonance imaging local invasion of veins can be identified more precisely. Most ACCs are greater than 4 cm when discovered. Since the liver, lungs, lymph nodes and bones are the most common sites of distant metastases, a CT thorax/abdomen is included in the diagnostic work-up. The role of FDG PET-CT needs to be further determined but studies using PET/CT to compare malignant lesions with adenomas show a high sensitivity, specificity, positive predictive value, and negative predictive value of 100%, 98%, 97%, 100%, respectively.⁸ Fine-needle aspiration biopsy is only recommended when an adrenal metastasis of another malignancy is suspected. For histopathological examination, the Weiss system is most commonly used.⁹ Ki67 proliferation index as determined using immuno/histochemistry has consistently been related to prognosis.¹⁰ Staging of ACC patients is performed with the ENSAT 2008 staging system.¹

At presentation, approximately 50% of adult patients have advanced stage III or IV disease.¹¹ In a palliative or metastasised setting mitotane monotherapy can be considered in patients with low-grade disease, late recurrence or those unfit to undergo chemotherapy. However, a survival benefit has not been proven.¹² Patients undergoing mitotane treatment can experience substantial toxicity, mostly gastrointestinal and neurological, also due to the small therapeutic range of this drug. For patients with aggressive tumours and WHO performance score 0-1, combination chemotherapy including etoposide, doxorubicin and cisplatin with mitotane is advised based on the FIRM-ACT trial that revealed a slight progression-free survival benefit of this regimen over streptozocin with mitotane.¹³ In case of Cushing's syndrome, tumour debulking or treatment with metyrapone or ketoconazole, next to the cortisol-lowering effects of mitotane, can be necessary to block adrenocortical cortisol synthesis.² Suppletion with hydrocortisone might be necessary on indication. Radiation therapy can be helpful in palliating pain. Overall, the prognosis of ACC is poor with a five-year survival of approximately 55 to 65% for early stage and 10 to 25% for advanced stage disease.¹⁴

Our case shows a rare cause of worsening of a pre-existing metabolic syndrome with sudden dysregulation of hypertension and diabetes as the clue to the underlying

cortisol-producing ACC. Cushing's syndrome is rare and the diagnosis is often delayed because part of its morbidity, namely the metabolic syndrome, has a high prevalence in the general population. The typical combination of Cushing's syndrome features or sudden worsening of symptoms should prompt the clinician to consider hypercortisolism as underlying cause. Since severe hypercortisolism can be lethal, it is essential to start appropriate treatment quickly.

DISCLOSURES

All authors declare no conflict of interest. No funding or financial support was received.

REFERENCES

- Fassnacht M, Arlt W, Bancos I, et al. Management of adrenal incidentalomas: European Society of Endocrinology Clinical Practice Guideline in collaboration with the European Network for the study of Adrenal Tumors. *Eur J Endocrinol*. 2016;175:G1-G34.
- Creemers SG, Hofland LJ, Korpershoek E, et al. Future directions in the diagnosis and medical treatment of adrenocortical carcinoma. *Endocr Relat Cancer*. 2016;23:R43-69.
- Lacroix A, Feelders RA, Stratakis CA, Nieman LK. Cushing's syndrome. *Lancet*. 2015;386:913-27.
- Giordano C, Guarnotta V, Pivonello R, et al. Is diabetes in Cushing's syndrome only a consequence of hypercortisolism? *Eur J Endocrinol*. 2014;170:311.
- Stewart PM, Walker BR, Holder G, O'halloran D, Shackleton CHL. 11 beta-Hydroxysteroid dehydrogenase activity in Cushing's syndrome: explaining the mineralocorticoid excess state of the ectopic adrenocorticotropin syndrome. *J Clin Endocrinol Metab*. 1995;80:3617.
- Van der Pas R, Leebeek FW, Hofland LJ, de Herder WW, Feelders RA. Hypercoagulability in Cushing's syndrome: prevalence, pathogenesis and treatment. *Clin Endocrinol (Oxf)*. 2013;78:481-8.
- 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.
- Metser U, Miller E, Lerman H, et al. 18F-FDG PET/CT in the evaluation of adrenal masses. *J Nucl Med*. 2006;47:32.
- Weiss LM, Medeiros LJ, Vickery jr AL. Pathologic features of prognostic significance in adrenocortical carcinoma. *Am J Surg Pathol*. 1989;13:202-6.
- Beuschlein F, Weigel J, Saeger, et al. Major prognostic role of Ki67 in localized adrenocortical carcinoma after complete resection. *J Clin Endocrinol Metab*. 2015;100:841-9.
- Fassnacht M, Johanssen S, Quinkler M, et al. Limited prognostic value of the 2004 International Union Against Cancer staging classification for adrenocortical carcinoma: proposal for a Revised TNM Classification. *Cancer*. 2009;115:243.
- Luton JP, Cerdas S, Billaud L, et al. Clinical features of adrenocortical carcinoma, prognostic factors, and the effect of mitotane therapy. *N Engl J Med*. 1990;322:1195.
- Fassnacht M, Terzolo M, Allolio B, et al. Combination chemotherapy in advanced adrenocortical carcinoma. *N Engl J Med*. 2012;366:2189-97.
- Icard P, Goudet P, Charpenay C, et al. Adrenocortical carcinomas: surgical trends and results of a 253-patient series from the French Association of Endocrine Surgeons study group. *World J Surg*. 2001;25:891.