

Image of the month: Diagnostic and therapeutic challenges in the management of ectopic ACTH syndrome: a perfect storm of hypercortisolism, hyperglycaemia and COVID-19

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ABSTRACT

Cushing's syndrome is a rare endocrine disorder requiring a high degree of clinical suspicion and meticulous investigations to diagnose and manage optimally. Delayed diagnosis and suboptimal treatment are associated with increased morbidity and mortality. Uncontrolled hypercortisolism leads to multiple cardiovascular and metabolic complications. Key risk factors identified for COVID-19-related adverse clinical outcomes (such as diabetes, hypertension and obesity) are, in fact, core clinical manifestations of Cushing's syndrome. Occurrence of SARS-CoV-2 infection in someone with uncontrolled hypercortisolism could, therefore, lead to disastrous medical consequences. We report a case highlighting challenges in the diagnosis and management of aggressive Cushing's syndrome secondary to ectopic adrenocorticotropic hormone (ACTH) secretion from an, as yet unidentified, neuroendocrine tumour. Our patient also contracted SARS-CoV-2 infection during investigations, which posed additional difficulties with aggravation of cardiometabolic complications. We also identify lack of clinical evidence to address management of this unique combination of two potentially life-threatening illnesses.

KEYWORDS: ectopic ACTH syndrome, hypercortisolism, hyperglycaemia, COVID-19

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Introduction

Cushing's syndrome is characterised by a constellation of clinical features and associated comorbidities caused by chronic exposure to excess glucocorticoids. While exogenous (iatrogenic) steroid use remains the common cause, endogenous hypercortisolism is rare, with an estimated incidence of 0.7–2.4 cases per million per year.¹ Broadly, hypercortisolism is categorised into adrenocorticotropic hormone (ACTH)-dependent versus independent causes with the latter primarily caused due to autonomous adrenal pathology.

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ACTH-dependent hypercortisolism due to pituitary adenoma (termed as 'Cushing's syndrome') remains the most common cause (80%) with the rest of the cases caused by ectopic ACTH or, more rarely, corticotropin releasing hormone (CRH) secretion.² In practice, confirming endogenous hypercortisolism and determining underlying cause is fraught with complexities and management challenges, even in the best of healthcare settings with many diagnoses delayed for months to years. This is, in part, due to non-specificity and variable manifestations of clinical features causing the patient to present to various specialties before the penny drops and correct diagnosis comes to the fore.

The case presented here came to the attention of the treating endocrinologist through a chance encounter outside of clinical settings. It led to stormy clinical course, posing complex diagnostic and therapeutic challenges in resource constrained settings amid a global pandemic, further complicated by SARS-CoV-2 infection and metabolic decompensation with eventual radical therapeutic measures leading to the path of recovery.

Case presentation

A 28-year-old man presented to the endocrine clinic with a 6-month history of rapid weight gain (approximately 20 kg), fatigue, generalised muscle and joint pains, intermittent headaches and low mood. Prior to presentation, he was seen by various physicians and received diagnoses of hypertension, pre-diabetes, depression and sleep apnoea. There was no other past medical history of note. He was not taking any regular medications and denied steroid use in any form. There was no drug allergy of note. He was married, worked as shopkeeper and smoked occasionally. There was no history of illicit drug usage. He had a family history of diabetes on paternal side.

Clinically, he displayed cushingoid features with rounded face, plethora, hyperpigmentation, acne and a supraclavicular fat pad (Fig 1a left). He also had abdominal adiposity with wide (over 3 cm) violaceous striae over the abdomen (Fig 1b). There was significant lower limb wasting with demonstrable proximal myopathy. Blood pressure was 150/90 mmHg, weight at 87 kg with height of 171 cm (body mass index (BMI) of 28 kg/m²).

He underwent 1 mg overnight dexamethasone test followed by 2 days of low-dose dexamethasone suppression test (LDDST), both of which failed to show suppression with cortisol levels of 979 nmol/L and 1,324 nmol/L, respectively (normal suppression



Fig 1. Photographs of presenting features. a) Left: Cushingoid features with rounded face, plethora, hyperpigmentation, acne and supraclavicular fat pad. a) Right: Before onset of symptoms for comparison. b) Abdominal adiposity with wide (over 3 cm) violaceous striae over the abdomen.

<50 nmol/L). ACTH level was high at 81.8 pg/mL (normal range (NR) 7–69), thus confirming ACTH-dependent hypercortisolism. Other tests showed glycated haemoglobin (HbA1c) at 7.5%, alanine aminotransferase (ALT) 55 U/L, hypertriglyceridemia 170 mg/dL (NR <150). Magnetic resonance imaging of the pituitary fossa did not reveal any obvious pituitary adenoma.

His presentation to the endocrine clinic coincided with the national lockdown due to global coronavirus pandemic in April and all routine hospital services were suspended at that time. He was started on ketoconazole 800 mg daily to control hypercortisolism.

Additionally, he was started on metformin 1 g twice daily (BD), gliclazide modified release 30 mg once daily (OD), atorvastatin 10 mg OD, escitalopram 10 mg OD, and amlodipine and valsartan combination of 5/160 mg OD. Inferior petrosal sinus vein sampling (IPSS) was planned as soon as interventional radiology services become operational.

Clinical progress

Repeat 24-hour urinary cortisol level, a month later, was 779 nmol (NR 138–690) and ALT was 86 U/L. Ketoconazole dose was increased to maximum tolerable dose of 1,200 mg daily.

In June, the patient developed persistent cough, shortness of breath and fever. RT-PCR came back positive confirming SARS-CoV-2 infection. He was admitted to the local hospital and managed as per national guidelines. He was categorised to have severe COVID-19 pneumonia. Key results are shown in Table 1.

He was treated with supplementary oxygen, broad spectrum antibiotics, methylprednisolone, prophylactic doses of enoxaparin and regular proning. He developed severe hyperglycaemia requiring high dose intravenous insulin infusions before switching to twice daily insulin regimen. Following discharge, he endured a protracted period of convalescence with fluctuating blood pressure, poorly controlled diabetes, severe fatigue and increased soft tissue swelling.

During endocrine review in September, he was noted to have further weight gain now reaching 96 kg (BMI 32.8 kg/m²), worsening abdominal adiposity and widespread limb bruising. He had also developed bilateral pedal oedema up to the shin. Repeat 24-hour urinary cortisol level was persistently high at 1,190 nmol with ALT 70 U/L.

He underwent desmopressin-stimulated IPSS which failed to demonstrate central to peripheral ACTH gradient, thus suggesting an ectopic source of ACTH secretion. Contrast-enhanced computed tomography (CT) of the chest, abdomen and pelvis did not show any obvious pathology apart from bulky adrenal glands. Due to local unavailability of nuclear scintigraphy, he was

Table 1. Key test results at time of admission with SARS-CoV-2 infection

Test	Results	Reference range
Interleukin 6, pg/mL	12.21	<7
C-reactive protein, mg/dL	96	<10
White cell count, × 10 ⁹ /L	15.6	4.0–11.0
Lymphocytes, %	17	20–40
Erythrocyte sedimentation rate, mm/Hr	26	1–13
Ferritin, µg/L	382.7	10–150
Lactate dehydrogenase, U/L	405	135–225
D-dimer, µg/mL	0.3	<0.4
Prothrombin time, seconds	12	11–13.5
Urea, mg/dL	15	5–20
Creatinine, mg/dL	1.01	0.84–1.21
Alanine aminotransferase, U/L	86	7–56

sent to another facility for Ga-68 DOTANOC positron emission tomography / CT. It also failed to reveal tracer avid lesion to account for ACTH secretion.

Clinically, the patient was in florid Cushing's syndrome with severe fatigue, rapid weight gain, worsening soft tissue oedema, erratic glucose control and muscle wasting. He was very depressed and also reported erectile dysfunction and low libido since initiation of ketoconazole.

Definitive treatment and outcome

Due to florid Cushing's syndrome with high risk of mortality, inadequate response to medical therapy and with no operable ectopic ACTH source, it was decided to proceed with bilateral adrenalectomy to rapidly ameliorate hypercortisolism. He underwent an uneventful laparoscopic procedure under perioperative steroid cover. He was discharged 3 days later with reducing schedule of prednisolone to maintenance daily dose of 5 mg with fludrocortisone of 100 µg.

At the 3-week postoperative review, there was a significant reduction in facial oedema with complete resolution of pedal oedema. Weight loss of 5 kg was noted compared with preoperative measurement. Fasting glucose was 5.7 mmol/L off anti-diabetic medications. Similarly, blood pressure was 130/80 mmHg off all antihypertensives. He reported improvement in muscle aches and energy level and had started to walk short distances unaided. Mentally he felt much better and had hoped to come off anti-depressants in the near future. He received education on sick day rules and advised to carry medic alert card. He will be followed up with interval imaging to identify the occult neuroendocrine tumour.

Discussion

Ectopic ACTH secretion (EAS) by various solid tumours of neuroendocrine origin makes up 10% to 20% of cases of ACTH dependent hypercortisolism.³ Over half of them are found in the lung and thymus with the most common being bronchial carcinoid tumours (over 25%) followed by small cell carcinoma (20%). Other sites of origin include medullary thyroid cancer, pheochromocytoma and islet cell tumours. Rarely extra thoracic non endocrine tumours may be the culprit.⁴ Differentiating EAS from pituitary source and localising lesion is crucial to guide definitive surgical treatment, since resection of adenoma or ectopic tumour has a high likelihood of clinical and biochemical cure. IPSS remains the most accurate test to differentiate between pituitary versus ectopic source of ACTH secretion.^{3,5} Localisation of ectopic tumour is another challenge necessitating application of various imaging modalities. Despite thorough radiological evaluation, substantial proportions of ectopic tumours remain unlocalised.^{6,7} In such cases, use of adrenolytic medications such as ketoconazole and metyrapone to control hypercortisolaemia and eventual adrenalectomy becomes main therapeutic strategy since adrenolytics are associated with significant side effects including serious liver dysfunction.⁸ Moreover, many ectopic tumours are indolent and may take as many as 20 years to be identified.⁴

There are some unique features to our case. It came at a time of global pandemic disrupting routine clinical services. While the European Society for Endocrinology (ESE) produced recommendations on the management of Cushing's syndrome during the pandemic with a focus on providing medical control

of hypercortisolism and deferring invasive procedures except in cases with high suspicion of EAS, there is no literature to guide management of SARS-CoV-2 infection with active Cushing's syndrome.⁹ Indeed, to the best of our knowledge, ours is the first case report of hypercortisolism secondary to EAS contracting SARS-CoV-2 infection.

Hypercortisolism is chronic inflammatory state with impaired innate and adaptive immunity predisposing patients to viral and other infections. While chronic hypercortisolism is associated with increased cytokine secretion which may be a risk for cytokine release syndrome and ARDS, the robust inflammatory response to acute infections is not always observed.^{10,11,12} One would speculate therefore that patients with Cushing's syndrome may have lower risk of acute respiratory distress syndrome development with SARS-CoV-2 infection, however, there is paucity of good quality data to confirm this. Moreover, cortisol excess associated comorbidities of obesity, diabetes and hypertension are recognised risk factors for adverse outcome in COVID-19.^{12,13} Additionally, data is rapidly accumulating in regards to severe insulin resistance, reduced insulin secretory capacity and metabolic decompensation with COVID-19.^{14,15}

The combination of Cushing's syndrome and concurrent SARS-CoV-2 infection is, therefore, a perfect storm requiring heightened vigilance in caring for this cohort of patients with meticulous attention to foresee and manage complications.

Further large-scale studies are required to add to the evidence and provide further clarity in our understanding of COVID-19 management and clinical outcomes in patients with active Cushing's syndrome. ■

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