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

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.

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...
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/m^2), 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

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**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. 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. 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. Localisation of ectopic tumour is another challenge necessitating application of various imaging modalities. Despite thorough radiological evaluation, substantial proportions of ectopic tumours remain unlocalised. In such cases, use of adrenolytic medications such as ketoconazole and metyrapone to control hypercortisolaemia and eventual adrenalectomy becomes main therapeutic strategy since eventual adrenalectomy to rapidly ameliorate hypercortisolism. He

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