CASE REPORT

Fountain of steroid from an ectopic ACTH-producing tumour

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SUMMARY

This case is of a 39-year-old Filipino woman who within 2 months developed, Cushing's features she had no known comorbidities and no history of steroid intake. The patient also presented with hyperpigmentation of knuckles and toes, metabolic alkalosis and persistent hypokalaemia noted as proximal muscle weakness. The patient was referred to our institution for acutely worsening behavioural and psychiatric changes. Work-up for endogenous Cushing's syndrome revealed a significant adrenocorticotrophic hormone production from an ectopic source. Further imaging was requested to locate the tumour, but the patient eventually succumbed to the drastic complications of hypercortisolism. On autopsy, the patient was found to have an ectopic well-differentiated neuroendocrine tumour located at the pancreatic head with metastasis to the right hepatic lobe.

BACKGROUND

Cushing's syndrome is a hormonal disorder caused by prolonged exposure of the body's tissues to high levels of the hormone cortisol. Typical signs and symptoms include upper body obesity, a rounded face, skin that bruises easily and heals poorly, weakened bones, excess body hair growth and menstrual irregularities in women and decreased fertility in men. It might be due to exogenous steroid use or an endogenous steroid overproduction from pituitary, adrenal or ectopic sources.¹

Majority of Cushing syndrome are due to exogenous glucocorticoids used in most inflammatory diseases. However, the less common endogenous Cushing syndrome has an annual incidence to be estimated at 13 cases per million individuals. Of these cases, approximately 70% are due to Cushing disease, that is, a pituitary adrenocorticotrophic hormone (ACTH) producing tumour, 15% are due to ectopic ACTH and the other 15% are due to a primary adrenal tumour.²

Some benign or, more often, cancerous tumours that arise outside the pituitary can produce ACTH. This condition is known as ectopic ACTH syndrome. Lung tumours cause more than half of these cases, and men are affected three times more often than women. The most common forms of ACTH-producing tumours are small cell lung cancer, which accounts for about 13% of all lung cancer cases and carcinoid tumours—small, slow-growing tumours that arise from hormone-producing cells in various parts of the body. Other less common types of tumours that can produce ACTH are thymomas, pancreatic islet cell tumours

and medullary carcinomas of the thyroid.¹ With its rarity, the ectopic ACTH syndrome discovered since 1961 will be presented and discussed to bring light into the clinical manifestations and laboratory findings in patients with endogenous hypercortisolism.

Figure 1 Physical findings: (A, B) hyperpigmented knuckles and toes; (C) acanthosis nigricans.

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Figure 2 Abdominal CT scan revealing a liver mass.

CASE PRESENTATION

A 39-year-old Filipino woman without any known comorbidities and with a good functional capacity was admitted at Philippine General Hospital presenting with agitation and hyperactivity. The initial impression was endogenous Cushing's syndrome probably from an endocrine secreting tumour of unknown origin.

The patient's condition started with a 2-month-history of progressive skin eruptions described as multiple hyperpigmented papules on the face and trunk, which were non-pruritic and non-tender. This was accompanied by gradual hyperpigmentation of armpits, neck area, knuckles and toes, acne formation, facial oedema, fat pad at the nape and supraclavicular area (figure 1). She was initially treated for urinary tract infection with unrecalled antibiotics.

After 1 month, she noticed worsening proximal muscle weakness leading to difficulty in ambulating. She was then admitted for productive cough, and thus was managed as a case of pneumonia treated for 1 week with antibiotics. On the same admission, she was observed to have persistent hypokalaemia, despite medical correction. She also reported right upper quadrant

discomfort, which prompted an abdominal CT scan showing multiple liver metastases of unknown primary (figure 2). She was discharged with further plans of working-up the liver masses, but she continued to have persistent hypokalaemia presenting as severe proximal muscle weakness affecting ambulation.

Few days prior to admission, she was observed to be confused and combative when awake, but appeared sleepy most of the time. She was also observed to have non-purposeful jerky movements, which were repetitive involving selected extremities. She was then brought to the hospital and was admitted.

Detailed physical examination showed features of Cushing's syndrome seen as moon facies, buffalo hump, plethora, acanthosis nigricans, acne formation, truncal obesity, muscle wasting and hyperpigmented knuckles and toes (figure 1). Initial vital signs showed elevated blood pressure, tachycardia, tachypnoea associated with irritable mood with note of purposeful jerky movement of extremities. External genitalia were unremarkable. Chest and abdominal findings were unremarkable.

INVESTIGATIONS

Several work-ups which were performed showed normal serum C3, negative anti-nuclear antibody, normal glycated haemoglobin A1C, hypokalaemia, abnormal thyroid function (low thyroid stimulating hormone and free triiodothyronine, normal free thyroxine), metabolic alkalosis, dyslipidaemia (high triglyceride, low high-density lipoprotein) and elevated liver enzymes.

Initial management for the patient was focused on establishing the diagnosis and aggressively providing supportive interventions and work-ups for expected complications. Endogenous Cushing's syndrome was confirmed with elevated serum cortisol and absence of normal suppression with 1 mg overnight dexamethasone suppression test. Further tests showed elevated serum ACTH, narrowing the differential diagnosis to either an ACTH-secreting pituitary tumour or an ectopic ACTH-producing tumour. Finally, failure to suppression of cortisol with high-dose dexamethasone pointed to an ectopic source (figure 3).

Figure 3 (A–C) Application of diagnostic algorithm and laboratory results.

(c)

DIFFERENTIAL DIAGNOSIS

When presented with a case of Cushing's syndrome, one must first confirm the diagnosis based on clinical signs and symptoms and screening tests (salivary cortisol, 24 h urine free cortisol, 1 mg dexamethasone suppression test). Exogenous steroid intake in any form must also be ruled out in the diagnosis of endogenous Cushing's. Once confirmed, three main differential sources would be considered: pituitary, adrenals and ectopic sources.

TREATMENT

While awaiting the establishment of the diagnosis, the patient was treated supportively for several complications brought about by hypercortisolism. These included antibiotics for anticipated nosocomial infection, insulin for secondary diabetes, anti-hypertensives (ACE-inhibitors) for secondary hypertension, aggressive electrolyte correction and sedatives for behavioural change.

OUTCOME AND FOLLOW-UP

The patient was admitted in the hospital for a total of 5 days until eventually succumbing to the complications of hypercortisolism (infection in an immunocompromised host). The patient's serum potassium remained persistently low despite aggressive intravenous potassium correction. Hyperglycaemia, hypertension and dyslipidaemia were adequately managed, but she eventually became septic leading to eventual shock and demise. Septic work-ups performed earlier showed growth of *Candida* from urine sample. The immediate cause of death was attributed to an acute fatal arrhythmia secondary to persistent electrolyte imbalance. The antecedent cause of mortality was septic shock because of nosocomial pneumonia and complicated urinary tract infection.

Autopsy revealed the presence of a neuroendocrine tumour located at the pancreatic head with metastatic lesions to the liver. Histological section of the tumour showed cellular components of small cells arranged in lobules separated by vascular fibrous septa with prominent vascular congestion with note of capsular invasion at the tumour pancreas interface. Looking closely, the tumour was composed of clusters of uniform round cells arranged in rosettes signifying a neuroendocrine differentiation (figure 4). Pathological and histological sections of the liver showed similar masses seen from the pancreas, which were confirmed to be metastatic lesions from the primary tumour seen at the pancreas (figure 5). Bilateral adrenal enlargement was observed. Pituitary gland, thyroid gland, spleen, heart and brain were all grossly normal. There was presence of pulmonary congestion due to concomitant pneumonia and necrotic changes from renal parenchyma because of previous urinary tract infection which gave light to the possible source of sepsis in our patient.

DISCUSSION

The association of Cushing's syndrome with tumours of non-pituitary and non-adrenal origin has been occasionally reported since the original description by Brown in 1928. Meador *et al* studied five patients with this syndrome and demonstrated the presence of ACTH-like activity in tumour tissues. This led to the postulation that these non-pituitary tumours elaborate ACTH-like materials causing hypercortisolism. This syndrome was then later referred as ectopic ACTH-producing tumour in 1963.³

Figure 4 (A–B) Histological section of pancreatic head showing a neuroendocrine tumour.

A case series of 30 patients by Imura⁴ showed bronchogenic cancer dominated the series. Other tumour sources included malignant epithelial thymoma, islet cell carcinoma of pancreas,

Figure 5 (A–B) Histological section of right hepatic lobe showing similar metastatic lesions from the pancreatic neuroendocrine tumour.

carcinoma of the oesophagus and squamous cell carcinoma of larynx. Lung, thymus and pancreas remained the main ectopic ACTH producers.

Patients with ectopic ACTH syndrome represent the broad clinical spectrum possible in Cushing's syndrome. Clinical presentation is most remarkable for weight loss, hypokalaemic alkalosis, hyperglycaemia and marked oedema. Hypokalaemic alkalosis is seen in 74–95% of patients with ectopic ACTH syndrome but in less than 10% of those with Cushing's disease.⁵ This is because of the higher cortisol levels seen in ectopic ACTH syndrome that overwhelm the 11- β -hydroxysteroid dehydrogenase enzyme, resulting in hypertension, oedema and hypokalaemia as a result of the mineralocorticoid effects of cortisol.⁶

Some patients may present with Cushing's syndrome rapidly leading to absence of typical physical findings found in classic Cushings. The patient may suffer immediately from complications of elevated cortisol levels due to the aggressiveness of the tumour secreting ACTH. Patients frequently suffer various psychological disturbances, ranging from euphoria to psychosis. Depression and anxiety are also common. Other signs include polyuria, persistent hypertension and insulin resistance, leading to hyperglycaemia which can lead to diabetes mellitus. Cushing's syndrome due to excess ACTH results in hyperpigmentation such as acanthosis nigricans in the axilla. This is due to melanocyte-stimulating hormone production as a by-product of ACTH synthesis from pro-opiomelanocortin. Cortisol can also exhibit mineralocorticoid activity in high concentrations, worsening the hypertension and leading to hypokalaemia.⁵

The diagnosis of endogenous Cushing's syndrome rests upon the association of the clinical features shown by the patient and demonstration of the absence of the normal circadian rhythm of plasma corticosteroids, absence of a corticosteroid response to an adequate degree of insulin-induced hypoglycaemia and resistance to suppression of plasma or urinary corticosteroids after administration of a low dose of dexamethasone (2 mg/day for 48 h). Differential diagnosis between the various causes of the syndrome is most reliably made by measurement of the plasma ACTH level; low or undetectable levels being found in patients with autonomous adrenocortical tumours while ACTH is present in the ACTH-dependent causes. Plasma ACTH levels in excess of 200 pg/mL suggest a diagnosis of the ectopic ACTH syndrome rather than Cushing's disease. Significant suppression of plasma or urinary corticosteroid levels during administration of a high dose of dexamethasone (8 mg/day for 48 h) is usually seen in patients with Cushing's disease but not in those with adrenocortical tumours or the ectopic ACTH syndrome. Algorithm for Cushing's syndrome can help clinicians easily in effectively diagnosing the cause of the endogenous source of hypercortisolism.² Our patient had an elevated baseline serum cortisol which was not suppressed with low and high dose overnight dexamethasone. Serum ACTH finally differentiated the cause to be from an ectopic ACTH-producing source.

A recent review of ectopic ACTH syndrome cases suggests that the preferred test to differentiate Cushing's disease from ectopic ACTH syndrome is inferior petrosal sinus sampling. A variety of imaging procedures are needed to localise ACTH-producing tumours. In a study made by Doppman,⁷ CT of the chest and abdomen was the most helpful study in the detection of these tumours. Selective arteriography (bronchial and visceral), systemic and portal venous sampling and iodine-131 meta-iodobenzylguanidine scintigraphy failed to

demonstrate tumours when findings at CT were negative. Bronchial carcinoids constituted most of the ACTH-secreting tumours in this study and in a review of four large series.

The treatment of the ectopic ACTH syndrome is often unavailing, since the tumour producing the ACTH is frequently highly malignant. If possible, the primary source should be removed after which plasma ACTH and corticosteroids may return to normal. If removal is not possible, then radiotherapy or chemotherapy may be used to give temporary relief; assay of plasma ACTH will provide a sensitive biochemical marker of the activity of the malignant disease and its response to therapy. Plasma corticosteroids can be effectively lowered using enzyme inhibitors such as metyrapone and aminoglutethimide, but this should be performed under dexamethasone cover until the correct dose of the inhibitor is discovered. If other treatments fail, surgical removal of the adrenal glands, called bilateral adrenalectomy, may replace drug therapy.^{2 4 5}

Learning points

- ▶ Early detection of tumour site and possible removal is of utmost importance in managing patients with ectopic adrenocorticotrophic hormone (ACTH) syndrome.
- ▶ Several clinical clues like metabolic alkalosis with severe hypokalaemia, behavioural change, hyperpigmentation, ecchymoses and short clinical course can be used to hasten diagnosis in patients with ectopic ACTH syndrome.
- ▶ Clinical diagnosis together with diagnostic algorithm can help and guide physicians in effectively diagnosing patients presenting with endogenous Cushing's syndrome.
- ▶ The lungs, gastrointestinal tract and pancreas remain to be the usual site of true ACTH-secreting tumours, although unique and peculiar sites such as the prostate, oesophagus and larynx might be a possibility.

Contributors TENL is the primary author and physician of the patient presented in this case. CAJ acted as the consultant of the service and editor of the said case report.

Competing interests None.

Patient consent Obtained.

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