An uncommon cause of Cushing’s syndrome in a 70-year-old man

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ABSTRACT
Cushing’s syndrome due to exogenous steroids is common, as about 1% of the general populations use exogenous steroids for various indications. Although endogenous Cushing’s syndrome due to ectopic adrenocorticotropic hormone from a pancreatic neuroendocrine tumour is rare, a correct and early diagnosis is important. The diagnosis and management require high clinical acumen and collaboration between different specialists. We report a case of ectopic adrenocorticotropic hormone Cushing’s syndrome due to pancreatic neuroendocrine tumour with liver metastasis. Early recognition by endocrinologists with timely surgical resection followed by referral to oncologists led to a favourable outcome for the patient up to 12 months after initial presentation.

Case report
In March 2013, a 70-year-old Chinese man presented with polyuria and polydipsia was diagnosed to have new-onset type 2 diabetes mellitus. He had suboptimal glycaemic control, and received multiple oral hypoglycaemic agents (OHAs). At the same time, he was noted to have bilateral lower limb pitting oedema and difficult to heal wounds over feet, as well as persistent hypokalaemia for which he was prescribed regular treatment with a potassium-sparing diuretic and oral potassium supplements. Symptoms and signs of Cushing’s syndrome (CS) including easy bruising, proximal muscle weakness, and central obesity were subsequently detected (Fig 1). He denied any history of taking herbal medicine or exogenous steroids. The overnight 1-mg dexamethasone screening test for CS yielded a non-suppressible plasma cortisol level of 1308 (reference level [RL], <50) nmol/L. Paired 9am cortisol and adrenocorticotropic hormone (ACTH)

FIG 1. Cushingoid features of the patient. (a) Patient’s front showing moon face and central adiposity; (b) patient’s back showing buffalo hump; (c) bruising over hand; (d) dependent oedema with poor wound healing over patient’s feet.
levels were 1220 nmol/L and 78 pmol/L (RL, <10.2 pmol/L), respectively. Two sets of values for 24-hour urinary free cortisol excretion were strikingly high at 2263 and 3601 nmol/day (reference range, 35-151 nmol/day). He also failed the confirmatory low-dose dexamethasone suppression test with a cortisol level of 997 nmol/L (RL, <50 nmol/L) after 2 days of dexamethasone loading. The peripheral corticotropin-releasing hormone (CRH) stimulation test later established the diagnosis of ectopic ACTH CS, since both the ACTH and cortisol responses were flat after CRH injection. Ketoconazole was commenced at that juncture, which was 2 months after the patient’s initial presentation.

Contrast computed tomography (CT) of the thorax and abdomen followed immediately, and revealed a well-defined ovoid cystic area (6.3 x 4.8 x 4.9 cm) with an intraslesional eccentric isodense mildly enhanced mural nodule in the body of pancreas that was consistent with pancreatic tumour, with enlarged lymph nodes posterior to the body of the organ (Figs 2a and 2b). Mild generalised osteoporosis was also noted. Positron emission tomography (PET) of the whole body 2 weeks later
showed a mildly hypermetabolic heterogeneous lesion in the body of the pancreas, compatible with the known pancreatic tumour. Also, there were mildly hypermetabolic lymph nodes in the peripancreatic region, possibly due to early nodal involvement. The serum CA19.9 level (a tumour marker of pancreatic cancer) was elevated (89 kIU/L; RL, <18 kIU/L).

The patient was referred to surgeons 3 months after initial presentation, and offered distal pancreatectomy with splenectomy (Figs 2c and 2d). Intra-operatively, a solitary 2-mm nodule over the undersurface of segment III of liver, not identified in the preoperative CT, was found and histologically confirmed to be metastatic neuroendocrine tumour (NET). Intra-operative ultrasound did not reveal any other liver lesions. There were no palpable lesions over whole length of small bowel or colon in the peritoneum or the omentum. Histology of the resected pancreatic mass confirmed the presence of malignant pancreatic NET (P-NET) with extrapancreatic extension and lymphovascular permeation. The tumour cells were diffusely positive for CK19, synaptophysin, and chromogranin. Staining for ACTH, gastrin, and pancreatic polypeptide were focally positive, but staining for insulin, serotonin, somatostatin, and glucagon were all negative. The proliferative pool as assessed by Ki-67 was estimated to be approximately 15%.

Postoperatively, ketoconazole was stopped, and the patient started taking replacement doses of hydrocortisone. He was then referred to an oncologist for further management in view of the metastatic nature of his disease (stage IV P-NET due to confirmed liver metastasis). One month after the operation, the patient experienced marked alleviation of his symptoms. He had no more oedema and the OHA requirements were significantly reduced.

Discussion

Cushing’s syndrome due to exogenous steroids is common, as about 1% of the general populations use exogenous steroids for various indications. Ectopic ACTH secretion accounts for approximately 10% to 20% of all cases of CS. The leading cause is small-cell lung carcinoma, accounting for about 50% of the cases. Other common tumours reported are pancreatic, bronchial, thymic, and thyroid medullary carcinoma. Others less common tumours reported are neuroendocrine tumours of the gastrointestinal tract, particularly gastrinoma and VIPoma. Between 5% and 15% of ACTH-secreting sources are ileal carcinoid tumours.

Other than insulinoma, these P-NETs are generally malignant. Those that are ACTH-producing (account for approximately 1.2% of them) are particularly aggressive. Metastases, usually to the liver, are often observed in early phase, even before the presentation of CS. The 2- and 5-year survival rates of patients with P-NETs are about 40% and 16%, respectively.

Symptoms and signs from excess cortisol, followed by biochemical evaluation and subsequent imaging, as in our patient, are important in the timely diagnosis of functioning P-NETs. In our patient, both the screening and other confirmatory tests for CS established the diagnosis. Non-suppressible/high ACTH in the presence of high serum concentrations and urinary secretion of cortisol, coupled with flat ACTH and cortisol responses after provocative peripheral CRH stimulation test, strongly suggested the CS was due to an ectopic ACTH-secreting source rather than the pituitary.

Other than the peripheral CRH stimulation test which offers 86% sensitivity and 90% specificity for pituitary CS, high-dose dexamethasone suppression test (HDDST) and bilateral inferior petrosal sinus (IPS) sampling for ACTH are two other options for differentiating pituitary CS and ectopic ACTH CS. A positive HDDST, characterised by suppression of serum cortisol by ≥50% from baseline by 8 mg of dexamethasone taken at 11 pm the night before, offers 77% sensitivity and 60% specificity for CS. The rationale for the use of HDDST is based on the principle that pituitary tumours are only partially autonomous, retaining feedback mechanism at a higher set point than normal. Therefore, when enough dexamethasone is administered, ACTH and cortisol secretion can be suppressed. While for ectopic ACTH tumours, which are usually autonomous, production of hormones cannot be suppressed with dexamethasone. However, some benign ectopic tumours may be suppressible, while pituitary macroadenomas are often non-suppressible. Whilst IPS sampling is invasive, it is the most direct way to examine whether the pituitary is the source of excess ACTH. An IPS/periphery ACTH ratio of ≥2.0 correctly identifies CS with 95% sensitivity and 100% specificity. The sensitivity is further improved to 100% when CRH is administered using the cut-off of post-CRH IPS/periphery ratio of ≥3.0.

In our case, immediate search for the ACTH-secreting source using CT and PET identified the pancreatic tumour promptly. Other imaging modalities commonly used in localising NETs include magnetic resonance imaging, endoscopic ultrasound, and somatostatin receptor scintigraphy. The source of ACTH in 30% to 50% of patients with ACTH-dependent CS is not localised by the conventional imaging modalities listed above. Newer imaging techniques such as fluorine-labelled dihydroxyphenylalanine (18F-DOPA) PET/CT are now being used to localise occult sources, although the usefulness of some of them remains controversial.
In a series of 17 patients, no advantage was seen with tumour localisation using (18F-DOPA) PET/CT when compared with conventional imaging, while another study reported 100% localisation of ectopic ACTH-secreting NETs using (18F-DOPA) PET/CT in three patients.9,10

Treatments for P-NETs include surgery, chemotherapy, radiotherapy, and interventional radiology techniques such as hepatic artery chemoembolisation. Surgery is the first-line option for resectable tumours and is also used for debulking metastatic tumours. Total hepatectomy with living donor transplantation has also been attempted for treating metastatic tumours.11 Somatostatin and its analogues have both antisecretory and antiproliferative effects.12 Although P-NETs are relatively radioresistant, recently developed peptide receptor radiotherapy employing radionuclide-targeted somatostatin receptor agonists for internal cytotoxic radiotherapy in somatostatin receptor-expressing NETs seem promising.12 Systemic therapies for unresectable tumours include sunitinib malate, a potent tyrosine kinase inhibitor with antiangiogenic effects, and everolimus, an inhibitor of mammalian target of rapamycin.12,13 After surgical resection of malignant P-NETs, Ki-67 >5% of tumour cells is a predictor of recurrence.5 Since our patient had a Ki-67 of approximately 15%, oncological treatment will be needed, hence, the referral.

In conclusion, our patient with an ectopic ACTH-secreting P-NET presented with diabetes and hypertension, both of which are common chronic diseases worldwide. Due to the aggressive nature of this type of tumour and its histological findings, this patient will likely require further adjuvant treatments in the future. Ectopic ACTH CS can occur due to a wide spectrum of causes, and a combination of relevant biochemical tests and imaging are needed to establish the correct diagnosis. Timely referral to surgeons and/or oncologists is necessary. Symptoms of hormone excess are often the first hint suggesting the diagnosis of functioning P-NETs. Almost all P-NETs, except insulinoma, carry a high malignant potential. Expeditious and meticulous management involving collaboration between endocrinologists, surgeons, pathologists, and oncologists can be expected to provide the best outcomes for patients suffering from this rare disease.

References