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Pancreatic Neuroendocrine Tumour as a Cause of Ectopic Cushing's Syndrome: A Rare Case Report

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Abstract

Pancreatic Neuroendocrine Tumors (pNETs) are rare neoplasms arising from the neuroendocrine islet cells of the pancreas and account for only 1% to 2% of all pancreatic malignancies. These tumors may secrete hormones; however 60% are considered 'non-functional' with no evidence of ectopic hormone secretion. Functional pNETs are known to secrete insulin, gastrin, glucagon, vasoactive intestinal peptide or somatostatin. A small number of the cases reported to date of this condition were typically for patients presenting with Cushing syndrome, where the tumor was discovered during investigations for the source of the ACTH. We report the case of a patient diagnosed with pNET initially believed to be non-functioning, who went on to develop features of ectopic ACTH syndrome (EAS).

This case highlights the importance of including cortisol and ACTH levels in screening for neuroendocrine activity in pancreatic tumors. An earlier screening and diagnosis could help ameliorating the patient's symptoms and halting disease progression.

Keywords: Cushing's syndrome; Ectopic Cushing's; Hypercortisolemia; Neuroendocrine tumor; Pancreatic neuroendocrine tumor

Introduction

Pancreatic Neuroendocrine Tumors (pNETs) are neoplasms arising from the neuroendocrine islet cells of the pancreas and account for only 1% to 2% of all pancreatic malignancies [1]. These tumors may secrete hormones; however 60% are considered 'non-functional' [2]. Functional pNETs are known to secrete insulin, gastrin, glucagon, vasoactive intestinal peptide or somatostatin. A small number of case reports have also identified pNETs secreting ACTH in patients who presented with clinical features of Cushing's syndrome. We report the case of a patient treated for a known pNET believed to be non-functioning, who went on to develop features of ectopic ACTH syndrome (EAS).

Case Presentation

A 59-year-old man with type 2 diabetes was diagnosed with a pNET following investigation for unintentional weight loss. The patient was then admitted to hospital for a subtotal pancreatectomy and splenectomy in addition to medical treatment with the Somatostatin analogue "Lanreotide". He had a complicated post-operative course and remained in hospital for an extended period due to recurrent infections, reduced mobility, confusion and hallucinations of unknown cause. During this time his blood pressure and blood glucose were persistently difficult to control.

Six months after surgery the patient was referred to hospital due to a routine blood test which had found neutrophilia with a White Cell Count (WBCs) of over 46.0 × 10^9/L. He complained of persistent fatigue and reduced mobility but had no other symptoms. A bone marrow biopsy indicated reactive changes but showed no evidence of a primary hematological diagnosis. He was also found to be hyperglycemic, hypokalemic with a plasma potassium of 3.1 mmol/L and his liver function was deranged with ALP 153 IU/L and ALT 233 IU/L. A recurrence of the pNET with evidence of lymphatic spread was found on CT.

Two months later the patient was readmitted with shortness of breath, cough and leg weakness. His mobility had significantly deteriorated, and he now required a wheelchair to mobilize. He was confused and complaining of hallucinations.

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Table 1: The patient's blood results.

Laboratory	Results	Reference range
Haemoglobin	136 g/L	130–180 g/L
Platelets	337 × 10^9/L	150–400 × 10^9/L
White cells	19.0 × 10^9/L	4–11 × 10^9/L
Neutrophils	17.64 × 10^9/L	2.0–7.5 × 10^9/L
Lymphocytes	0.67 × 10^9/L	1.0–4.5 ×10^9/L
Monocytes	0.61 × 10^9/L	0.3–0.9 × 10^9/L
Sodium	142 mmol/L	135–145 mmol/L
Potassium	3.4 mmol/L	3.5–5.3 mmol/L
Calcium (corr.)	2.47 mmol/L	2.2–2.6 mmol/L
Urea	4.0 mmol/L	2.5–6.7 mmol/L
ALP	323 IU/L	30–130 IU/L
ALT	48 IU/L	5–35 IU/L
Glucose	11.0 mmol/L	3.5–5.5 mmol/L

ALP: Alkaline Phosphatase; ALT: Alkaline Transaminase

He also had increased oxygen requirement, thin skin, and reduced tone and sensation in the lower limbs. The patient had persistent hypokalemia. His blood glucose, WBCs and LFTs also remained elevated (Table 1). A whole spine MRI ruled out cord compression but showed degenerative changes and multiple fractures of the vertebrae. A chest CT revealed consolidation and a new sternal fracture.

Despite improvement of the chest infection after treatment, the patient continued to suffer with confusion, fatigue, poor mobility as well as intractable hypertension, hyperglycaemia and hypokalemia. Tests were, therefore, carried out to screen for Cushing's syndrome (Table 2). These results are indicative of ACTH-dependent Cushing's syndrome.

A pituitary MRI was carried out, which did not find evidence of a pituitary lesion. Inferior petrosal sampling would normally be carried out to definitely exclude a pituitary source of ACTH; however the patient was not eligible for this invasive procedure due to his poor functional status. As a result of the known neuroendocrine tumour, the very high ACTH level and the persistent hypokalemia, a diagnosis of ectopic ACTH Cushing's syndrome secondary to metastatic pNET was made. The patient was started on Metyrapone, a reversible inhibitor of 11β-hydroxylase which blocks cortisol biosynthesis, with dexamethasone on a block and replace regimen. He also received a prophylactic treatment for Pneumocystis jiroveci in addition to prophylactic anti-coagulation.

Since initiation of treatment, the patient's quality of life has greatly improved. He has had a significant reduction in the frequency of infections, his blood sugars have improved, his blood pressure is now well controlled on Spironolactone and he has regained some mobility. However, a recent CT has found marked enlargement of the pNET recurrence and he is now being considered for peptide receptor radionucleotide therapy.

Discussion

We report a rare case of EAS in a patient with a complicated post-operative course after the resection of a pNET.

Most of the cases reported to date of this condition were for patients presenting with Cushing syndrome, where the tumour was discovered during investigations for the source of the ACTH.

Table 2: Screening for Cushing's syndrome.

Laboratory	Results	Reference range
Mid night Cortisol	1583 nmol/L	(normal <50 nmol/L)
ACTH	534 pg/mL	normal range 10-60 pg/mL
Overnight dexamethasone suppression test: Cortisol level	1314 nmol/L	normal <50 nmol/L

We therefore wish to highlight the importance of including cortisol and ACTH levels in screening for neuroendocrine activity in pancreatic tumors. This patient had many of the complications related to Cushing's syndrome and an earlier screening and diagnosis could have helped ameliorating his symptoms and halting disease progression.

Diagnosis of functional pNETs is typically guided by clinical symptoms and confirmed by elevated plasma levels of the hormone [1]. An ACTH-secreting pNET will lead to clinical presentation with Cushing's syndrome. These patients present with a variety of Cushing features such as truncal obesity, hirsutism, bruising, striae, muscle weakness and wasting, fatigue, mood disturbance, recurrent infection, hypertension, osteoporosis and hyperglycaemia [3-5]. One case series of ACTH-secreting pNETs reported patients presenting with hypokalemia and severe fatigue before the classical symptoms of Cushing's syndrome, which they suggest is due to a rapid increase in serum cortisol [6].

Cushing's syndrome can be screened for using midnight cortisol levels, urinary free cortisol, dexamethasone suppression test and salivary cortisol. If hypercortisolism is confirmed, serum basal ACTH should be measured to differentiate ACTH-dependent or independent causes.

ACTH-dependent Cushing's syndrome is most commonly caused by pituitary adenomas [7]. This should be investigated by pituitary imaging, inferior petrosal sinus sampling and Corticotropin-Releasing Hormone (CRH) tests. The CRH test would show a marked rise in cortisol in pituitary-dependent disease compared to ectopic disease [4,7]. Cross-sectional imaging studies and somatostatin receptor scintigraphy can be used to localize tumors which may be an ectopic source of ACTH hypersecretion [1]. Central and ectopic sources of ACTH may also be differentiated by plasma ACTH level (typically very high in ectopic disease), high-dose dexamethasone suppression test (basal cortisol suppression more likely in pituitary-dependent disease) and serum potassium (hypokalemia nearly always seen in ectopic disease).

Management of functioning pNETs requires treatment for both the hormone-excess state and the tumour itself. Surgical removal of the tumor is essential as malignant behavior is reported in >50% of pNETs [1]. Where surgery is ineffective in controlling hormone hypersecretion, medical treatment is essential in reducing morbidity and mortality. Suppression of cortisol hypersecretion can be achieved with inhibitors of steroidogenesis such as metyrapone, mitotane and ketoconazole [8,9]. While these agents offer rapid control of hypercortisolism, there is a risk of cortisol "escape" with long-term use [10]. The somatostatin analogue pasireotide may be beneficial in these patients through its direct anti-tumors effects [8,9]. Peptide receptor radionucleotide therapy has also been identified as helpful in controlling EAS [8].

Conclusion

This case highlights the importance of considering and screening

for ACTH-dependent Cushing's syndrome in patients with pNETs especially if they present with non-specific symptoms.

References

1. Ito T, Igarashi H, Jensen RT. Pancreatic neuroendocrine tumors: Clinical features, diagnosis and medical treatment: Advances. Best Pract Res Clin Gastroenterol. 2012;26(6):737-53.
2. Alexakis N, Neoptolemos JP. Pancreatic neuroendocrine tumours. Best Prac Res Clin Gastroenterol. 2008;22(1):183-205.
3. Kondo T, Matsuyama R, Ashihara H, Matsuo Y, Saski K, Goto R, et al. A Case of ectopic adrenocorticotropic hormone-producing pancreatic neuroendocrine tumor with multiple liver metastases. Endocr J. 2010;57(3):229-36.
4. Patel FB, Khagi S, Daly KP, Lechan RM, Ummaritchot V, Saif MW. Pancreatic neuroendocrine tumor with ectopic adrenocorticotropin production: A case report and review of literature. Anticancer Res. 2013;33(9):4001-5.
5. Sayesteh S, Fouladi DF, Fishman EK, Kawamoto S. Ectopic crushing syndrome caused by a pancreatic neuroendocrine tumor: A case report. Radiol Case Rep. 2020;15(7):1014–7.
6. Zhang C, Jin J, Xie J, Ye L, Su T, Jiang L, et al. The clinical features and molecular mechanisms of ACTH-secreting pancreatic neuroendocrine tumors. J Clin Endocrinol Metab. 2020;105(11):dgaa507.
7. Trainer PJ, Grossman A. The diagnosis and differential diagnosis of Cushing's syndrome'. Clin Endocrinol (Oxf). 1991;34(4):317-30.
8. Ito T, Lee L, Jensen RT. Treatment of symptomatic neuroendocrine tumor syndromes: Recent advances and controversie. Expert Opin Pharmacother. 2016;17(16):2191-05.
9. Creemers SG, Hofland LJ, Lamberts SWJ, Feelders RA. 'Cushing's syndrome: An update on current pharmacotherapy and future directions'. Expert Opin Pharmacother. 2015;16(12):1829-44.
10. Cuevas-Ramos D, Lim DST, Fleseriu M. 'Update on medical treatment for Cushing's disease'. Clin Diabetes Endocrinol. 2016;2:16.