

Cushing's Syndrome Accompanied with Adrenal and Pancreatic Mass: A Case Report

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Cushing's syndrome results from inappropriate excessive endogenous glucocorticoids secretion. It may be due to ACTH-producing pituitary adenoma, Adrenocortical adenoma, iatrogen glucocorticoid use, or ectopic ACTH production. Patients, who remain untreated, have high morbidity and a significant mortality. We describe a very challenging case of Cushing's syndrome due an adrenal adenoma on a pancreatic mass.

Material and Methods: A 20-year-old woman presented with sign and symptoms of Cushing syndrome. Thorough basal and dynamic hormonal assessment. In addition, the results of imaging studies are presented.

Results: The source of ACTH secretion was adrenal adenoma, and hypercortisolism was controlled by adrenalectomy. A unique feature of this case is the fact that we observed an adrenal adenoma as a source of Cushing syndrome and an incidental nonfunctional pancreatic nesidioblastosis.

Conclusion: The diagnosis of Cushing's syndrome may turn out to be sometimes a complex and time-consuming challenge in clinical endocrinology.

Key Words: Cushing's syndrome, Pancreatic tumor

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Introduction

A 20-year-old woman presented with a 6 kg weight gain over 6 months (mostly abdominal), muscle weakness, hirsutism, acne, ankle edema, polydipsia, nocturia, diabetes, fatigue, pigmentation, depression and amenorrhea to Taleghani Hospital in July 2006. She was referred to an endocrinologist because of suspected Cushing's syndrome. She did not smoke tobacco, and gave no history of taking recreational drugs or alcohol or glucocorticoids. In her physical examination, she was grossly Cushingoid with thin skin, round and plethoric face, acne and hirsutism, supraclavicular and interscapular fat pads, purple striae on the abdomen, ecchymoses and hyperpigmentation in both shins, and had proximal myopathy. Her blood pressure was 170/100. The patient was taken off diuretics and initial investigations revealed hypokalemia with alkalosis. Chest x-ray revealed left pleural effusion. The basal urine free cortisol and low-dose dexamethasone suppression test (LDDST); 2 mg dexamethasone per day for 48 h) confirmed Cushing's syndrome. After a high-dose dexamethasone suppression test (HDDST; 8 mg dexamethasone per day for 48 h), she failed to suppress 09:00 h cortisol by more than 50% and urine free cortisol was 180 µg/24

hours. ACTH was detectable at levels of 66 pgr/ml and 48 ng/L on two consecutive mornings. The diagnosis of Cushing's syndrome was given.

Pituitary CT scan showed no lesion. Chest CT scan was normal except for the presence of pleural effusion, while abdominal CT scan revealed right adrenal mass and another mass at the head of the pancreas. Although the results of the HDDST test suggested the possibility of right adrenal mass as a source of cortisol secretion, we were concerned about the pancreatic mass as a suspicious source of cortisol secretion; however ketoconazole was commenced before surgery. Elevated blood sugar levels were managed by insulin therapy. Despite this treatment, biochemical control was suboptimal, and the patient's condition deteriorated and necessitated right adrenalectomy and exploration of the pancreatic mass. During operation, a 1.5 cm right adrenal mass and a 6. cm mass in the head of pancreas was found, but left adrenal was normal. Pathologic examination of the adrenal specimen revealed adrenal adenoma, and pancreatic mass showed the pancreatic parenchyma alteration of the endocrine component in the form of hyperplasia of the islets. Variation in the size and number of islets was striking, and many showed irregular outlines. There was budding of ducts, forming the ductular-insular complexes characteristic of nesidioblastosis. On IHC-staining, no ACTH was detected in pancreatic tumor cells.

The patient was discharged on post-operative day ten without complications. All symptoms related to disease resolved up to 4 weeks after surgery. Normal menstrual period was obtained. She no longer needed insulin therapy. She returned to normal daily activity. On extended follow-up, every 6-12 months, blood sugar level, serum cortisol level and UFC remained normal and the patient is well without any problem 2 years after surgery.

Discussion

This case is the first report of Cushing's syndrome with an accidental non-functional nesidioblastosis.

Cushing's syndrome results from inappropriate excessive endogenous glucocorticoids secretion. Patients, who remain untreated, have high morbidity and a significant mortality.¹ The syndrome remains a challenge to diagnose and manage. The most common cause is excessive adrenocorticotrophin (ACTH) production, due to pituitary microadenoma, but adrenal adenoma and ectopic ACTH production, are less often causes of endogenous Cushing's syndrome.² The incidence rate of Cushing's syndrome caused by unilateral adrenal adenoma is estimated at 2 cases per 1,000,000 population per year. Factitious administration of glucocorticoids have also been reported.³ Some cases of Cushing's syndrome due to rare causes such as functioning adrenocortical oncocytoma of the adrenal cortex or paraneoplastic Cushing's syndrome because of corticotrophin-releasing hormone-secreting Wilms' tumor have been reported.⁴⁻⁵ Cushing's syndrome has many difficulties in diagnosing and managing.⁶⁻⁷ According to the Endocrine Society Clinical Practice Guidelines, after excluding exogenous glucocorticoid use, initial use of one test with high diagnostic accuracy (urine cortisol, late night salivary cortisol, 1 mg overnight or 2 mg 48-h dexamethasone suppression test) is recommended. Patients who have abnormal results, should be visited by an endocrinologist and undergo a second test, either one of the above or, in some cases, a serum midnight cortisol or dexamethasone-CRH test. Then patients are divided into two groups, and those with abnormal results undergo testing for Cushing's syndrome and patients with normal results do not need further evaluation.⁸ According to the high dose dexamethasone suppression test, the most probable cause of Cushing's syndrome was adrenal adenoma; however we were concerned about the pancreatic

mass, as another source for cortisol overproduction.

After thorough histopathology examination, we found that pancreatic mass was a nonfunctional nesidioblastosis.

The term "nesidioblast" (islet builder) was described by Laidlaw in 1938, who selected the Greek word for islet, nesidion, and blastos to designate the cells that differentiate from ductal epithelium and bud from ducts to form new islets. It contains insulin producing cells, distributed through parenchyma, and may be local or diffuse.^{9,10} Adult nesidioblastosis is a rare disease,^{11,12} and to our knowledge there are 142 cases described in literature over three-quarters of a century.¹³⁻¹⁵ The usual presentation of this condition is related to hypoglycemia, with symptoms such as sense of hunger, tremor, dizziness, diaphoresis or seizures or loss of consciousness.¹⁶ Clinically it is the same as insulinoma, and is diagnosed surgically and confirmed by histopathology. Hypoglycemia, secondary to nesidioblastosis is rare in adults and the pathogenesis, of this condition is unknown.¹¹ Our patient had no signs or symptoms, related to hypoglycemia; however she had hypergly-

cemia as one of the signs of Cushing's syndrome, signifying that nesidioblastosis was non-functional in this patient. Although it was confirmed that all nesidioblastosis induce hyperinsulinemia,¹⁷⁻²⁰ and subsequently hypoglycemia, Jaffe et al, first questioned this role. They reported a series of 32 normoglycemic infants with nesidioblastosis.¹⁴ Rumilla et al reported 36 normoglycemic cases of nesidioblastosis by immunohistochemistry. They used antibodies to insulin-like growth factor1, and 2 (IGF1- IGF 2), transforming growth factor-beta 1 and 2, insulin-like growth factor one receptor-alpha epidermal growth factor receptor, and transforming growth factor-beta receptor type 3.¹⁵

Nesidioblastosis does not have any role in inducing symptoms of Cushing's syndrome in this case, because in IHC-staining no ACTH producing cells were confirmed. We found this pathologic finding accidentally during surgery confirmed by histopathology as nesidioblastosis.

To conclude, the diagnosis of Cushing's syndrome may turn out to be sometimes a complex and time-consuming challenge in clinical endocrinology.

References

1. Terzolo M, Bovio S, Reimondo G, Pia A, Osella G, Borretta G, et al. 2005 Subclinical Cushing's syndrome in adrenal incidentalomas. *Endocrinol Metab Clin North Am* 2005; 34: 423-39.
2. Morris DG, Grossman AB. Dynamic tests in the diagnosis and differential diagnosis of Cushing's syndrome. *J Endocrinol Invest* 2003; 26 Suppl 7: 64-73.
3. Kaltsas GA, Giannulis MG, Newell-Price JD, Dacie JE, Thakkar C, Afshar F, et al. A critical analysis of the value of simultaneous inferior petrosal sinus sampling in Cushing's disease and the occult ectopic adrenocorticotropin syndrome. *J Clin Endocrinol Metab* 1999; 84: 487-92.
4. Nieman LK. Difficulty in the diagnosis of Cushing disease. *Nat Clin Pract Endocrinol Metab* 2006; 2: 53-7.
5. Nieman LK, Biller BM, Findling JW, Newell-Price J, Savage MO, Stewart PM, et al. The diagnosis of Cushing's syndrome: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2008; 93: 1526-40.
6. Laidlaw GF. Nesidioblastoma, the islet tumor of the pancreas. *Am J Pathol* 1938; 14: 125-34.
7. Fong TL, Warner NE, Kumar D. Pancreatic nesidioblastosis in adults. *Diabetes Care* 1989; 12: 108-14.
8. Jabri AL, Bayard C. Nesidioblastosis associated with hyperinsulinemic hypoglycemia in adults: review of the literature. *Eur J Intern Med* 2004; 15: 407-10.
9. Fong TL, Warner NE, Kumar D. Pancreatic nesidioblastosis in adults. *Diabetes Care* 1989; 12:108-14.
10. Karnauchow PN. Nesidioblastosis in adults without insular hyperfunction. *Am J Clin Pathol* 1982; 78: 511-3.

11. Jaffe R, Hashida Y, Yunis EJ. Pancreatic pathology in hyperinsulinemic hypoglycemia in infancy. *Lab Invest* 1980; 42: 356-65.
12. Rumilla KM, Erickson LA, Service FJ, Vella A, Thompson GB, Grant CS, et al. Hyperinsulinemic hypoglycemia with nesidioblastosis: histologic features and growth factor expression. *Mod Pathol*. In press 2008.
13. Kenney B, Tormey CA, Qin L, Sosa JA, Jain D, Neto A. Adult nesidioblastosis. Clinicopathologic correlation between pre-operative selective arterial calcium stimulation studies and post-operative pathologic findings. *JOP* 2008; 9: 504-11.
14. Brown RE, Still WJ. Nesidioblastosis and the Zollinger-Ellison Syndrome. *AM J Dig Dis* 1968; 13: 656-63.
15. Tsujino M, Sugiyama T, Nishida K, Takada Y, Takanishi K, Ishizawa M, et al. Noninsulinoma pancreatogenous hypoglycemia syndrome: a rare case of adult-onset nesidioblastosis. *Intern Med* 2005; 44: 843-7.
16. Won JG, Tseng HS, Yang AH, Tang KT, Jap TS, Lee CH, et al. Clinical features and morphological characterization of 10 patients with noninsulinoma pancreatogenous hypoglycaemia syndrome (NIPHS). *Clin Endocrinol (Oxf)* 2006; 65: 566-78.
17. Service FJ, Natt N, Thompson GB, Grant CS, van Heerden JA, Andrews JC, et al. Noninsulinoma pancreatogenous hypoglycemia: a novel syndrome of hyperinsulinemic hypoglycemia in adults independent of mutations in Kir6.2 and SUR1 genes. *J Clin Endocrinol Metab* 1999; 84: 1582-9.