

AN INTRACTABLE CASE OF INSULINOMA

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Abstract

We had experienced an intractable case of insulinoma to diagnose and treat. A 53-year-old, obese woman had suffered unconsciousness on exercise as hypoglycemic attack about once a month for 5 years. The oral glucose tolerance test, glucagon test, tolbutamide test, 1-leucine test and bonito insulin suppression test showed abnormalities not in insulin but in plasma blood sugar level (hypoglycemia). Fasting hypoglycemia and positive sign of fasting test for 43.5 hours were obtained. Glucose-tolbutamide-glucagon test elevate serum insulin level from 9 to 289 μ U/ml. Absence of insulin release in response to calcium was obtained in the patient. A tumor stain (about 1.1 cm in diameter) was revealed at the tail of the pancreas by coeliacography, but computerized tomography was of little value in this case. A solitary adenoma (1.5 \times 1.3 \times 1.1 cm, about 1 g) was removed surgically. The histological findings were B-cell adenoma of type IV with amyloid deposition. After surgery, hypoglycemic episodes disappeared completely.

INTRODUCTION

Organic hyperinsulinism is a possible diagnosis in any patient with bizarre behavior or disturbances of consciousness that arise primarily in the fasting state. Simultaneous estimation of fasting blood glucose and insulin on three consecutive days may show clear enough increases in insulin/glucose ratios to establish the diagnosis of organic hyperinsulinism¹⁾. But in our case, the fasting insulin level was almost normal (9-16 μ U/ml), though the fasting blood sugar level was low (30-60 mg/dl). Otherwise, satisfaction of Whipple's triad was obtained. Therefore, the coeliacography was performed and presented the

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tumor stain at the tail of the pancreas. A case of insulinoma with almost normal levels of serum insulin and hypoglycemia was reported.

MATERIALS AND METHODS

Case Report

The patient is a 53-year-old woman whose occasional unconsciousness and bizarre behavior have been about once a month for 5 years. Blood sugar levels from that period are unknown, and she has consulted for a local doctor for these periods. The occasional unconsciousness and bizarre behavior do not disappear. The local doctor transferred her to the Division of Endocrinology of Kawasaki Medical School Hospital.

The findings on physical examination were normal, besides obesity (height 148 cm ; weight 60 kg).

Routine laboratory tests were also normal except for fasting serum glucose levels of 30 to 60 mg/dl.

Clinical Tests

Standard clinical methods were used for the tolerance tests for glucose (50-g administered orally), glucagon (1.0-mg intravenously), tolbutamide (1.0-g intravenously) and 1-leucine (12-g orally). Each test was carried out after the patient had fasted for 15 hours overnight. And fasting test was also taken for 43.5 hours.

To assess the insulin response to calcium and exogenous insulin, a calcium infusion test (4-mg Ca^{2+} /kg/hr) and bonito insulin suppression test (0.2 U/kg subcutaneously) were performed²⁻⁴, and serum immunoreactive insulin (IRI), serum C-peptide immunoreactivity (CPR) and plasma glucose were measured at various intervals. Glucose (100-g orally)-tolbutamide (1-g intravenously)-glucagon (1-mg intravenously) test was done and plasma glucose and serum IRI were also measured over a one-and-half-hour period.

Coeliacography was performed by our colleagues in Department of Radiology. Computerized tomogram was obtained with OHIO Nuclear Delta 190.

The extirpation of the pancreatic tail tumor was performed by our colleagues in Department of Surgery. The histology of the tumor was evaluated by our colleagues in Department of Pathology.

After surgery, the glucose tolerance test, tolbutamide test and glucose-tolbutamide-glucagon test were performed with the same methods as before.

Plasma sugar level was estimated by glucose-oxidase method with Glucose Analyser (IATRON, Model M-7000). The levels of IRI and CPR were measured by the method of Horino et al.⁵ and that of Kaneko et al.⁶, respectively. Calcium level was measured by O-CPC method of Connerty et al.⁷.

RESULTS

Hypoglycemic symptoms and signs were apparent in this case, but any positive results were hardly obtained from several endocrinological tests, besides the results of low blood sugar levels as shown in table 1.

TABLE 1. Insulin, C-peptide and Glucose Responses during in vivo Tests before Surgery

Test	Time (Min)									
	0	5	30	45	60	90	120	180	240	360
Oral glucose tolerance										
plasm glucose (mg/dl)	52		145		131	111	55	40	38	45
serum insulin (μ U/ml)	9		44		29	23	14	19	14	9
Glucagon tolerance										
plasm glucose (mg/dl)	34	36	97	110	107					
serum insulin (μ U/ml)	10	13	30	29	34					
Tolbutamide tolerance										
plasm glucose (mg/dl)	37	36	22	25						
serum insulin (μ U/ml)	9	45	21	19						
serum CPR (ng/ml)	1.7	4.0	2.5	2.2						
l-leucine tolerance										
plasm glucose (mg/dl)	56		17	12	8					
serum insulin (μ U/ml)	21		24	27	22					
serum CPR (ng/ml)	1.9		2.1	2.8	2.8					
Ca infusion										
plasm glucose (mg/dl)	59		32		30	23	18	26		
serum insulin (μ U/ml)	16		20		23	22	17	14		
serum CPR (ng/ml)	2.6		3.2		3.2	3.0	3.4	2.7		
serum Ca (mEq/L)	4.8		4.7		4.7	4.6	4.7	4.6		
Insulin tolerance										
plasm glucose (mg/dl)	39		53		53	44	28			
serum insulin (μ U/ml)	9		12		12	25	25			
serum CPR (ng/ml)	1.5		1.8		1.4	2.4	2.2			
Glucose-tolbutamide-glucagon tolerance										
plasm glucose (mg/dl)	40	148	114		100	113				
serum insulin (μ U/ml)	9	258	159		80	70				
					Time (Hr)					
		0	18	24	38	42	43.5			
Fasting										
plasm glucose (mg/dl)	94		56	36	31	34	26			

Coeliacography was performed and demonstrated a small faint tumor stain in the lower border of the pancreatic tail. At the same time, several blood samples were taken through the catheter, but the levels of serum IRI were within normal.

TABLE 2. Insulin, C-peptide and Glucose Responses during in vivo Tests after Surgery

Test	Time (Min)							
	0	5	30	45	60	90	120	180
Oral glucose tolerance								
plasm glucose (mg/dl)	88		157	175	163	119	81	69
serum insulin (μ U/ml)	7		77	80	66	12	6	5
serum CPR (ng/ml)	2.0		7.7	10.2	9.7	6.4	3.9	2.8
Tolbutamide tolerance								
plasm glucose (mg/dl)	83	83	55	48	54	63	65	
serum insulin (μ U/ml)	7	59	17	11	8	7	6	
serum CPR (ng/ml)	1.9	5.1	3.5	3.3	3.1	2.4	1.4	
Glucose-tolbutamide-glucagon tolerance								
plasm glucose (mg/dl)	82	159	107	92	80	85	63	
serum insulin (μ U/ml)	6	204	109	102	59	54	30	
serum CPR (ng/ml)	1.9	21.6	11.9	11.7	10.9	7.1	5.4	



Fig. 1. Electromicrographic study of the tumor

There are few granules in these cells which show the invagination between cells and have some desmosome.

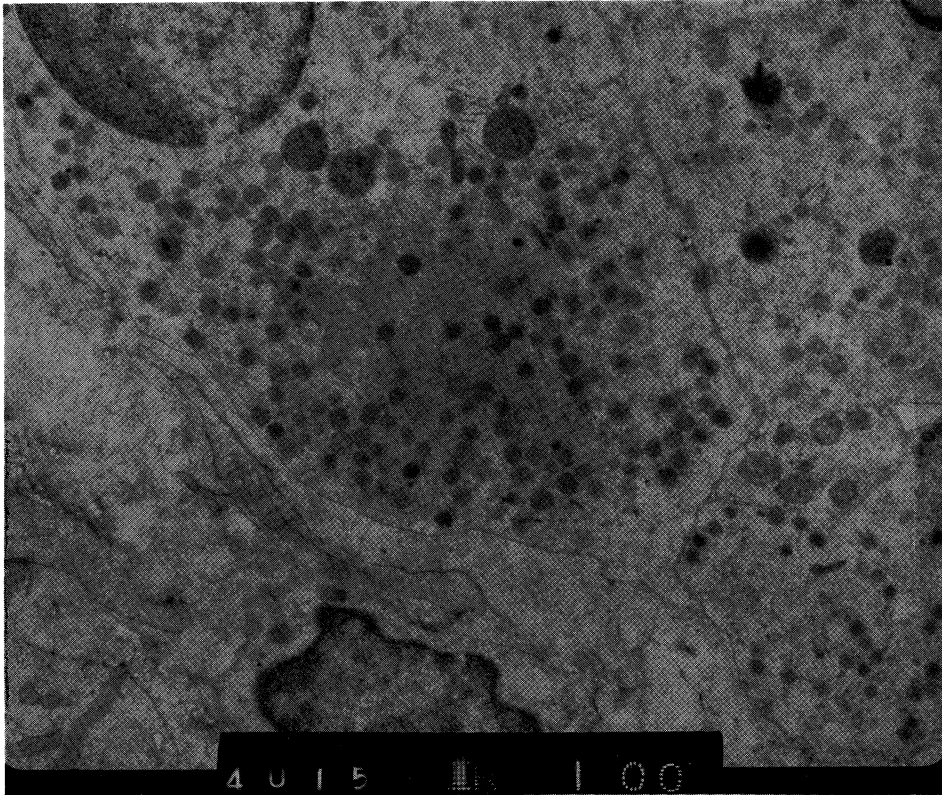


Fig. 2. Electromicroscopic study of the tumor
There are round granules in several stages of their maturity.
Desmosome is also revealed.

A tumor which was located at the tail of pancreas was encapsulated firmly ($1.5 \times 1.3 \times 1.1$ cm, 1.0 g).

In our microscopic and electromicroscopic studies of the tumor, there were many cells without secretory granules. In a few cells with granules, the round one was exclusively recognized as shown in Fig. 2. And the invagination between cells and some desmosome were apparently revealed as shown in Fig. 1. From these findings of the pathology, the tumor was classified benign B-cell adenoma which was of the type IV, according to Creutzfeldt et al.⁸⁾

After surgery, the results of a few tests were essentially normal and hypoglycemic attacks were completely disappeared.

DISCUSSION

Organic hyperinsulinism has to be managed step by step at diagnosis.

Organic hyperinsulinism is a possible diagnosis in any patient with bizarre behavior or disturbances of consciousness that arise primarily in the fasting state. Simultaneous estimation of fasting blood glucose and insulin on three consecutive days may show clear enough increases in insulin/glucose ratios to establish the diagnosis of organic hyperinsulinism¹⁾.

In our case, the levels of serum insulin were always low, though the plasma glucose levels were also low. But the insulin/glucose ratio showed a tendency of high level. Other several tests showed the low levels of plasma glucose, not accordingly to the levels of IRI in serum. A calcium infusion test is said to stimulate insulin release selectively from insulin secreting tumors^{2,9)}. But the case did not show the apparent release of insulin, though the plasma glucose level went down, after the load of calcium. From above mentioned results, the insulin release was poor but the blood glucose level was always low not proportionally to the level of insulin. These facts suggested the possible diagnosis of insulinoma¹⁾. In calcium infusion test, the release of insulin was not revealed. The histological findings of the tumor could be a kind of benign insulinoma as reported by Pointel et al⁴⁾.

Preoperative localization of tumors greatly increases the chance of a successful first operation, because of its small size. In a study from the Mayo Clinic 30 out of 34 (90%) insulinomas discovered at operation had been satisfactorily localized by angiography¹⁰⁾, though computerized tomography was of little value⁹⁾. But a British group reports that angiography never accurately localized a tumor which was not palpable at operation¹¹⁾. In one large series 40% were less than 1.0 cm and 65% less than 1.5 cm in diameter. Therefore our case belongs to a major group in size, but the tumor which has few secretion granules in cytoplasm could be hardly diagnosed.

When an insulinoma is diagnosed, operation is usually recommended ; and at operation the chances of success are greatly enhanced if the tumor can be identified.

We had experienced an intractable case of insulinoma to diagnose. Because the tumor belongs to the type IV according to Creutzfeldt et al.,⁸⁾ and effects of various stimuli on release of insulin in vivo were nearly normal. Therefore the serum insulin level is always low not proportionally to plasma sugar levels.

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REFERENCES

- 1) Turner, R. C., Oakley, N. W. and Nabarro, J. D. N. : Control of basal insulin secretion with special reference to the diagnosis of insulinomas. *Br. Med. J.* **i** : 132-135, 1971
- 2) Gaeke, R. F., Kaplan, E. L., Rubenstein, A., Starr, J. and Burke, G. : Insulin and proinsulin release during calcium infusion in a patient with islet-cell tumor. *Metabolism* **24** : 1029-1034, 1975
- 3) Roy, B. K., Abuid, J., Wendorff, H., Nitiyanant, W., DeRubertis, F. R. and Field, J. B. : Insulin release in response to calcium in the diagnosis of insulinoma. *Metabolism* **28** : 246-252, 1979
- 4) Pointel, J. P., Villaume, C., Gay, G., Drouin, P. and Debry, G. : Absence of effect of calcium perfusion on blood sugar and plasma insulin in a patient with a benign insulinoma. *Horm. Metab. Res.* **10** : 572-573, 1978
- 5) Horino, M., Machlin, L. J., Hertelendy, F. and Kipnis, D. M. : Effect of short chain fatty acids on plasma insulin in ruminant and nonruminant species. *Endocrinology* **83** : 118-128, 1968
- 6) Kaneko, T., Oka, H., Munemura, M., Oda, T., Yamashita, K., Suzuki, S., Yanaihara, N., Hashimoto, T. and Yanaihara, C. : Radioimmunoassay of human proinsulin C-peptide using synthetic human connecting peptide. *Endocrinol. Japon.* **21** : 141-145, 1974
- 7) Connerty, H. V. and Briggs, A. R. : Determination of serum calcium by means of orthocresolphthalein complexone. *Am. J. Clin. Path.* **45** : 290-296, 1966
- 8) Creutzfeldt, W., Arnold, R., Creutzfeldt, C., Deuticke, U., Frerichs, H. and Track, N. S. : Biochemical and morphological investigations of 30 human insulinomas. *Diabetologia* **9** : 217-231, 1973
- 9) Kaplan, E. L. and Lee, C. H. : Recent advances in the diagnosis and treatment of insulinomas. *Surg. Clin. North. Am.* **59** : 119-129, 1979
- 10) Fulton, R. E., Sheedy, P. F., McIlrath, D. C. and Ferris, D. O. : Preoperative angiographic localization of insulin-producing tumors of the pancreas. *A. J. R.* **123** : 367-377, 1975
- 11) LeQuesne, L. P., Nabarro, J. D. N., Kurtz, A. and Zweig, S. : The management of insulin tumors of the pancreas. *Br. J. Surg.* **66** : 373-378, 1979