

# A Case of Proinsulin-Secreting Malignant Insulinoma in an Elderly Patient with Cerebral Infarction

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## Abstract

The diagnosis of insulinoma is sometimes challenging and the symptoms of hypoglycemia may be overlooked in elderly patients with cerebrovascular diseases and higher cerebral dysfunction. Recently, there have been an increasing number of case reports of insulinoma secreting proinsulin without hyperinsulinemia. We report a case of proinsulin-secreting malignant insulinoma in a 72-year-old man with aphasia due to cerebral infarction. He manifested no apparent symptoms, although he was incidentally found to have recurrent hypoglycemia by plasma glucose measurements. The Fajans, Grunt and Turner indexes were all within normal range and the arterial stimulation and venous sampling (ASVS) test revealed no increase in insulin concentration. However, proinsulin concentration was markedly elevated (2470 pmol/l) and well-differentiated endocrine adenocarcinoma, malignant insulinoma, with 2 cm in size in the tail of the pancreas was surgically removed.

The diagnosis of hypoglycemia requires careful attention especially in elderly persons and/or patients with cerebrovascular diseases. Measurement of proinsulin is recommended in the diagnosis of insulinoma without hyperinsulinemia.

**Keywords:** Malignant insulinoma; Hypoglycemia; Taminato index; Proinsulin

## Introduction

Insulinoma is an islet beta cell-derived tumor manifesting various clinical symptoms due to hypoglycemia. However, the diagnosis of insulinoma is sometimes challenging and overlooked in patients with higher cerebral dysfunction such as elderly patients with cerebrovascular diseases, since their complaint of hypoglycemia is often unclear. Recently, there have been an increasing number of cases with insulinoma secreting proinsulin without hyperinsulinemia. Here we report a case of proinsulin-secreting malignant insulinoma in an elderly patient with aphasia due to cerebral infarction.

## Case Report

A 72-year-old man with aphasia due to cerebral infarction lived in a nursing home. His hypoglycemia, plasma glucose 31 mg/dL, was incidentally found and repeated examination revealed his recurrent hypoglycemia without apparent symptoms. He was referred to our hospital for investigation and laboratory studies showed fasting plasma glucose, 50 mg/dl and fasting serum immunoreactive insulin (IRI), 14.7  $\mu$ U/ml and prominently elevated proinsulin concentration (2470 pmol/l, Human Proinsulin RIA kit, Linco Research). The Fajans, Grunt and Turner indexes, diagnostic indicators of insulinoma, were all negative, and only the Taminato index was positive (585; insulinoma > 280) (Table 1). Mild response of insulin secretion was observed in 75g oral glucose tolerance test (OGTT) and no response of insulin secretion in the glucagon stimulation tests (Figure 1a and b).

Abdominal dynamic computed tomography (CT) demonstrated an enhanced tumor about 2 cm in size in the tail of the pancreas in the early phase (Figure 1c). Celiac angiography showed tumor staining in the area of the pancreas tail (Figure 1d). In the arterial stimulation and venous sampling (ASVS) test, the serum concentrations of insulin obtained from the right hepatic vein revealed no increase after the

injection of calcium gluconate (0.025 mEq/kg) into the proximal splenic artery (Figure 1e).

The spleen preserving distal pancreatectomy was performed upon diagnosis of insulinoma confirmed in the pancreas tail. Histological findings of the resected pancreatic tumor revealed tumor cells with anisokaryosis and invasion to the prepancreatic fat tissue (Figure 2a and b). Immunohistochemistry for insulin showed positive staining in tumor cells (Figure 2c) and the MIB-1 labeling index was 5% (Figure 2d), indicating well-differentiated endocrine adenocarcinoma; malignant insulinoma.

After the surgery, recurrent hypoglycemia disappeared. Abnormal findings identified in 75g OGTT and the glucagon stimulation test revealed normal response (Figure 1a and b).

## Discussion

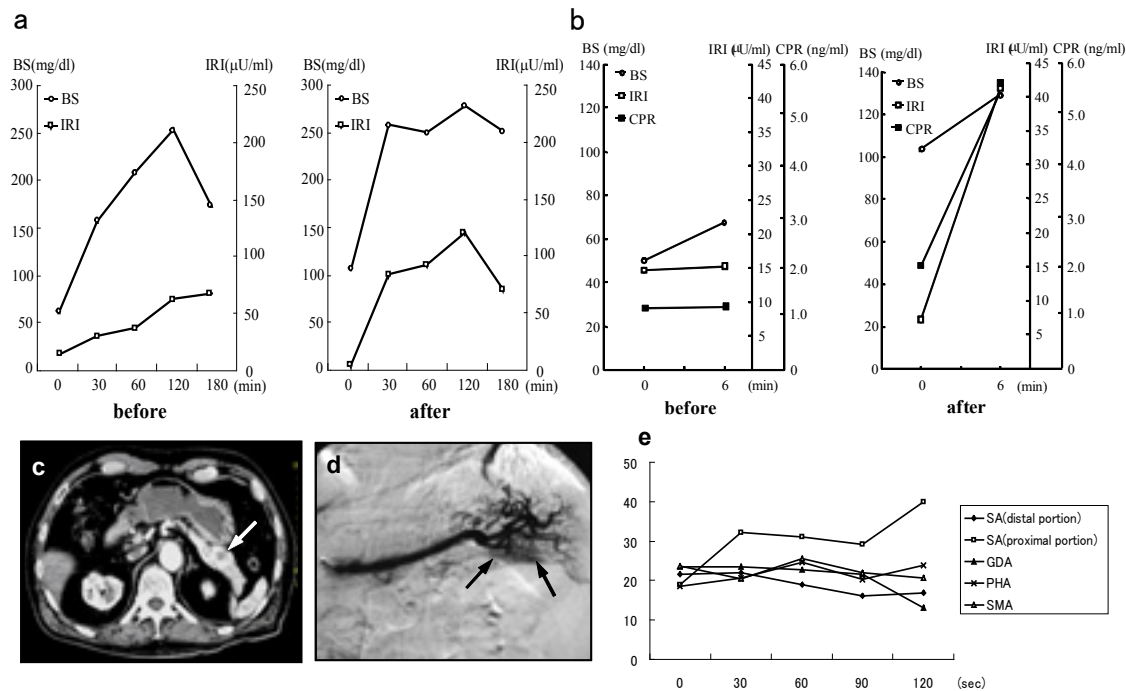
There has been the reported cases of insulinoma without hyperinsulinemia and the importance of measurement of proinsulin is noted [1-3]. Tsuzuki and Ishii [4] reported that the levels of serum IRI were less than 20  $\mu$ U/ml in 46% of patients and 18% of those showed negative Fajans index in the review of 358 cases of insulinoma. In this case of proinsulin-secreting insulinoma, the Fajans, Grunt and Turner

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**Received** July 16, 2010; **Accepted** August 30, 2010; **Published** August 30, 2010

**Citation:** Furushima K, Tone A, Katayama A, Iseda I, Higuchi C, et al. (2010) A Case of Proinsulin-Secreting Malignant Insulinoma in an Elderly Patient with Cerebral Infarction. J Diabetes Metab 1:103. doi:10.4172/2155-6156.1000103

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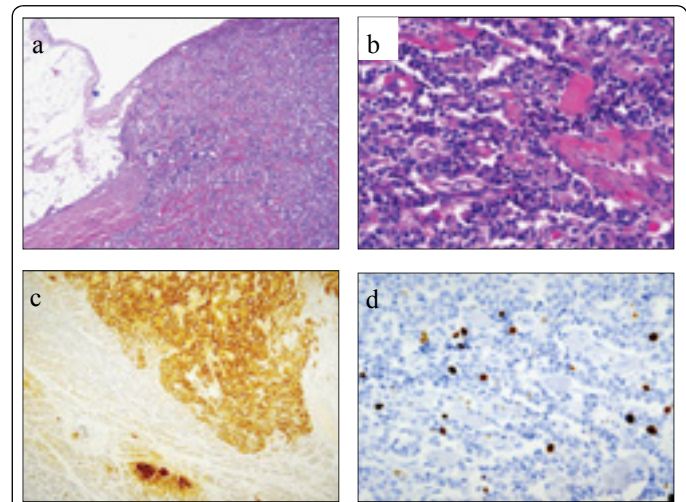
SA: splenic artery, GDA: gastroduodenal artery, PHA: proper hepatic artery, SMA: superior mesenteric artery

**Figure 1:** Results of 75gOGTT (a) and glucagon stimulation test (b) before and after surgery. Abdominal dynamic computed tomography (c) demonstrated an enhanced tumor (arrow) in the tail of the pancreas in the early phase. Celiac angiography (d) showed tumor staining (arrow) in the area of the pancreas tail. The arterial stimulation and venous sampling (ASVS) test (e) showed that the serum concentrations of insulin obtained from the right hepatic vein were slightly increased after the injection of calcium into the proximal splenic artery.

CBC		Glycemic control and insulin secretion	
WBC	3600 / $\mu$ l	FPG	50 mg/dl
RBC	434 $\times 10^4$ / $\mu$ l	HbA1c	5.0 %
Hb	13.8 g/dl	s-CPR	1.2 $\mu$ g/ml
Hct	41.1 %	U-CPR	21.9 $\mu$ g/day
Plt	20.2 $\times 10^4$ / $\mu$ l	IRI	14.7 $\mu$ U/ml
Chemistry		Hormone examination	
TP	6.6 g/dl	GH	1.0 U/ml
Alb	3.8 g/dl	PRL	9.1 U/ml
T-Bil	0.7 mg/dl	ACTH	320 JDF units
AST	34 IU/l	Cortisol	5.5 %
ALT	57 IU/l	fT3	2.3 pg/ml
LDH	197 IU/l	fT4	1.06 ng/dl
ALP	188 IU/ml	TSH	1.25 $\mu$ U/ml
$\gamma$ -GTP	30 IU/l	TPOAb	2.4 IU/ml
BUN	16 mg/dl	TgAb	11.4 IU/ml
Cr	1.12 mg/dl	Adrenaline	52 pg/ml
UA	7.9 mg/dl	Noradrenaline	459 pg/ml
Na	140 mEq/l	Dopamine	9 pg/ml
K	4.4 mEq/l	Glucagon	124 ng/dl
Cl	108 mEq/l	Tumor marker	
Amylase	176 IU/l	CEA	2.0 ng/ml
Lipase	33 IU/l	CA19-9	<2.0 U/ml
T-cho	177 mg/dl	AFP	3.3 U/ml
HDL-C	33 mg/dl	DUPAN2	<2.5 U/ml
LDL-C	129 mg/dl	SPAN1	2.6 U/ml
TG	87 mg/dl	Index	
CRP	0.2 ng/ml	Fajans index*	0.29
Urinalysis		Grunt index**	3.40
pH	7.0	Turner index†	73.5
Glu	-	Taminato Index‡	585
Prot	-		
OB	-		
Keton	-		

\*Fajans Index:  $IRI/BS > 0.3$  \*\*Grunt Index:  $BS/IRI < 2.5$  †Turner Index:  $(IRI \times 100)/(BS - 30) > 200$  ‡Taminato Index:  $(100 - BS) \times (IRI - 3) > 280$

**Table 1:** Laboratory data on admission.



**Figure 2:** (a) Histological findings of the pancreatic tumor (hematoxylin-eosin staining, low-power field). (b) Histological findings of tumor cells with anisokaryosis (hematoxylin-eosin staining, high-power field). (c) Immunohistochemistry using antibody against insulin showed positive staining in tumor cells and normal islet cells of the pancreas (insulin stain, low-power field). (d) Immunohistochemical staining for MIB-1 (high-power field). The labeling index was 5%.

indexes were all negative and only the Taminato index was positive, although it revealed mild elevation of serum insulin levels.

An increasing number of case reports of insulinoma with elevated levels of proinsulin has been accumulated since the first case report by Melani et al. [3], Alsever et al. [1] also reported a case of hypoglycemia coexisting with low plasma IRI and high serum

proinsulin concentrations and they suggested that the difference in the methods of IRI measurement contributed to low plasma IRI levels in islet-cell tumor. Currently, fluorescent immunoassay, which has very low cross-reactivity to proinsulin, is commonly performed, resulting in the identification of an increasing number of the cases of insulinoma without apparent hyperinsulinemia. In current case, the levels of IRI were measured by fluorescent polarization immunoassay (FPIA) using monoclonal antibodies, which showed very low cross-reactivity to proinsulin, *i.e.* 0.016%. Diagnostic criteria for insulinoma, such as the Tuner index, are not always applicable with IRI levels measured using monoclonal antibodies, since they were established when polyclonal antibodies were used. Given the situation where monoclonal antibodies are widely used, it is suggested that the Taminato index is more helpful for diagnosis than others.

In summary, we report a case of proinsulin-secreting malignant insulinoma in an elderly patient with cerebral infarction. In this case, there were no apparent symptoms of hypoglycemia. The

diagnosis of hypoglycemia requires careful attention especially in elderly persons and patients with cerebrovascular diseases, since their complaint of hypoglycemia is often unclear. Measurement of proinsulin is recommended in the diagnosis of insulinoma without hyperinsulinemia.

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