

## A Rare Case of Adult-onset Nesidioblastosis Treated Successfully with Diazoxide

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**Abstract.** A 54-year-old man was admitted to our hospital for evaluation of hypoglycemia. He had frequent episodes of loss of concentration before dinner. The ratio of IRI to plasma glucose (PG) was 0.8–1.0. Abdominal CT revealed no pancreatic tumor, and angiography of splenic artery showed no definite tumor stain within the pancreas. Based on the results of selective arterial calcium stimulation and hepatic venous sampling (ASVS), the provisional diagnosis was a small insulinoma in the pancreatic body. The patient underwent subtotal distal pancreatectomy. However, histopathological and immunohistochemical examinations of the resected tissue showed hypertrophy of islets of Langerhans islands and  $\beta$  cells around pancreatic ducts. The final diagnosis was adult-onset nesidioblastosis. Postoperatively, the patient continued to exhibit hyperinsulinemia and nighttime hypoglycemia. Octreotide, voglibose and diet therapies failed to improve the nocturnal hypoglycemia. However, treatment with diazoxide at a starting dose of 200 mg/day resulted in immediate amelioration of nocturnal hypoglycemia. This is the first Japanese adult case of nesidioblastosis treated successfully with diazoxide. This case report suggests that diazoxide may be effective for adult-onset nesidioblastosis in a manner similar to that described for pediatric cases.

**Key words:** Hypoglycemia, Adult-onset nesidioblastosis, ASVS, Diazoxide

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**NESIDIOBLASTOSIS** is the most common cause of hyperinsulinemic hypoglycemia in infants [1]. The pathological substrate is characterized by diffuse or disseminated proliferation of islet cells arising from pancreatic ducts or ductules [2]. If untreated, severe hypoglycemia in nesidioblastosis can lead to brain damage or death in infants. The condition is rarely seen in adults with hyperinsulinemic hypoglycemia [3]. The current available treatments for nesidioblastosis are pancreatectomy and medication, such as diazoxide, octreotide and corticosteroid. Diazoxide evolved first as an antihypertensive agent with vasodilatory action on peripheral arterioles. It was later found to inhibit insulin secretion from pancreatic  $\beta$  cells and reduce

stimulation-evoked catecholamine release by opening ATP-sensitive  $K^+$  channels, with the inhibition of insulin leading to increased glucose output from the liver [4–8]. Here we report a rare case of nesidioblastosis in an adult patient who was successfully treated with diazoxide.

### Case Report

A 54-year-old man was admitted to our hospital in June 2003 for evaluation of hypoglycemia. He had been diagnosed with impaired glucose tolerance in 1999. Since June 2002, he experienced occasional episodes of loss of concentration before dinner, which gradually increased in frequency to almost daily episodes in March 2003. The symptom improved with supplementary diet. Because fasting hypoglycemia was identified in May 2003, he was admitted to a local hospital for further examination of hypoglycemia.

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Medical examination showed fasting plasma glucose of 59 mg/dl and IRI of 59  $\mu$ U/ml, indicating hypoglycemia without suppression of insulin secretion. The patient was referred to our hospital for evaluation of hypoglycemia. The family history was unremarkable apart from a diabetic mother. The mother did not have any episode of a hypoglycemia or unconscious attack in her early history. On admission, the consciousness level was clear, body temperature was 35.3°C, pulse rate was 66/min (regular), and blood pressure was 130/80 mmHg. Height was 167 cm and body weight 71 kg (body mass index: 25.5 kg/m<sup>2</sup>). General examination was negative including that of the breasts and abdomen. There was no peripheral edema and neurological examination was normal. Laboratory studies on admission (Table 1) showed hypoglycemia (46 mg/dl) and unsuppressed immunoreactive insulin (IRI) level (18.7  $\mu$ U/ml). A standard oral glucose tolerance test (75g OGTT) showed a high basal level of IRI relative to plasma glucose concentration before glucose loading. Furthermore, although 75g OGTT demonstrated a pattern of diabetes mellitus (DM), IRI was abnormally high and plasma glucose level was low at 300 minutes after glucose loading (Table 2). Insulin-counter regulatory hormones, such as glucagon, catecholamine and cortisol, increase glucose level in hypoglycemia. However, during the hypoglycemia in this case, insulin-counter regulatory hormones were not elevated, suggesting reduced sensitivity of the hypoglycemic response by the long-term exposure to hypoglycemia. The serum IRI/plasma glucose (PG) ratio was 0.8–1.0. Abdominal CT showed no pancreatic tumor, and an-

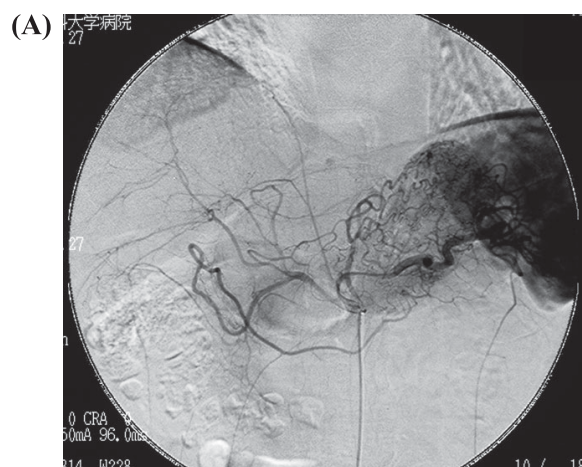
giography of splenic artery showed no definite tumor staining. Finally, selective arterial calcium stimulation and hepatic venous sampling (ASVS) showed a brisk response of plasma insulin level in both the splenic and superior mesenteric arteries (Fig. 1). Somatostatin and

**Table 2.** Endocrinological examination

Daily profile				U-CPR 83.3 mg/day			
Time	7:00	11:30	17:30	20:30	7:00		
PG (mg/dl)	51	89	70	95	29		
75g OGTT							
Time (min)	0	30	60	120	180	240	300
PG (mg/dl)	46	159	211	201	140	80	53
IRI (mU/ml)	18.7	94.6	76.3	51.5	41.9	11.2	19.6
Hypoglycemia							
PG	46 mg/dl		Cortisol		15.7 mg/dl		
IRI	18.2 mg/dl		Adrenalin		240 pg/ml		
Glucagon	256 pg/ml		Noradrenalin		759 pg/ml		
ACTH	104 pg/ml		Dopamine		24 pg/ml		
GH	1.0 ng/ml		Insulin antibody		5.3%		

**Table 1.** Laboratory findings on admission

Urine		Biochemistry	
pH	5.0	TP	7.6 g/dl
Protein	(–)	AST	26 IU/l
Glucose	(–)	ALT	42 IU/l
Ketone	(–)	$\gamma$ -GTP	56 IU/l
O.B.	(–)	ALP	221 U/l
		LDH	147 IU/l
CBC		Amy	87 IU/l
WBC	9,800/ml	T-Cho	179 mg/dl
RBC	534 $\times$ 10 <sup>4</sup> /ml	TG	138 mg/dl
Hb	15.8 g/dl	BUN	12 mg/dl
Ht	47.1%	Cre	0.9 mg/dl
Plt	21.4 $\times$ 10 <sup>4</sup> /ml	Na	143 mEq/l
		K	3.6 mEq/l
		Cl	108 mEq/l
		FPG	46 mg/dl



**(B)**

		Time (sec)			
		0	30	60	90
IRI (mU/ml)	Gastroduodenal artery	15.3	22.5	21.1	19.1
	Superior mesenteric artery	30.4	145.0	237.0	162.0
	Splenic artery	62.3	64.6	51.2	50.6

**Fig. 1.** Angiography and hepatic venous sampling. (A) Angiography of the splenic artery showed no definite tumor staining. (B) Hepatic venous sampling showed stimulation of plasma insulin both in the splenic and superior mesenteric arteries.

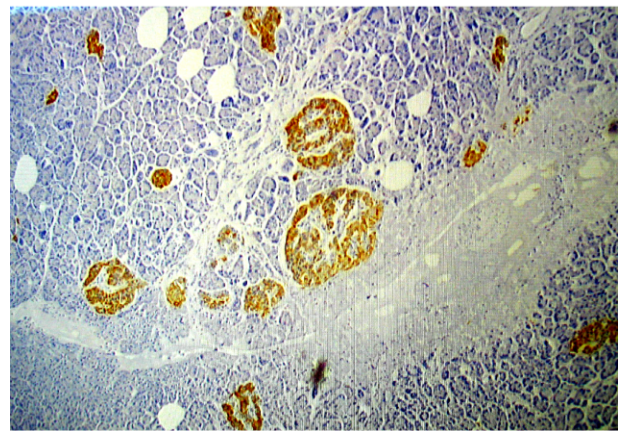
glucagon loading tests were performed for the purpose of adaptation to treatment. The former test did not show hyperglycemia after loading and the latter test showed temporary hyperglycemia (Table 3).

Based on the above findings, the provisional diagnosis was a small insulinoma in the pancreatic body. Accordingly, the patient underwent subtotal distal pancreatectomy after obtaining an informed consent. Pathological examination of the resected tissue showed hypertrophy of islets of Langerhans islands and immunohistological staining revealed  $\beta$  cells around pancreatic ducts (Fig. 2). Based on these clinicopathological features, the final diagnosis was adult-onset nesidioblastosis. However, insulin hypersecretion did not improve after surgery ( $IRI/PG = 1.17$ ) and nighttime hypoglycemia continued after the operation. Treatment with octreotide, corticosteroid and voglibose as well as supplementary diet failed to improve the nocturnal hypoglycemia (plasma glucose: 30–50 mg/dl). The sleeping disorder of nocturnal hypoglycemia negatively influenced the quality of life. Because there were no other therapeutic tactics available to improve the nocturnal hypoglycemia apart from diazoxide, we finally chose to use diazoxide. After obtaining an informed consent, diazoxide treatment was started at 200 mg/day and the dosage was gradually increased. Although hypoglycemia improved, facial flushing, edema and weight increase were noted with 600 mg/day of diazoxide. Finally, we gradually reduced the dose of diazoxide from 600 to 350 mg/day and combined it with voglibose before dinner. This treatment resulted in amelioration of nocturnal hypoglycemia and other symptoms. Although blood pressure slightly decreased from 140/78 mmHg to 120/70 mmHg after starting diazoxide treatment, the patient had no other side effects such as dizziness. The latest 75 g OGTT under the continued use of diazoxide and voglibose showed suppression of insulin hypersecretion (Table 4). Since hyperinsulinemia was suppressed after the treatment, insulin action as indexed by HOMA-R was considered to have improved and beta cell function as indexed by insulinogenic index was suppressed. Furthermore, beta cell function seemed to be retained as indexed by urine CPR value after the treatment. Therefore, we suspect that the risk of developing diabetes mellitus in the future is low.

**Table 3.** Somatostatin loading test (subcutaneous octreotide 100 mg) and glucagon test

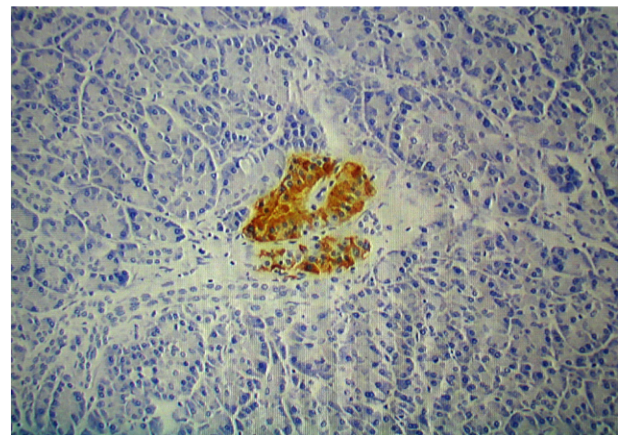
Somatostatin loading test (octreotide 100 mg s.c.)							
Time (min)	0		60		120		
PG (mg/dl)	40		24		25		
IRI (mU/ml)	12.5		49.5		17.4		
Glucagon test							
Time (min)	0	1	6	10	15	30	60
PG (mg/dl)	30	54	80	93	93	73	52
IRI (mU/ml)	15.8	22.2	45.8	67.8	71.7	40.6	12.1

(A)



100  $\mu$  m

(B)



25  $\mu$  m

**Fig. 2.** Histopathological examination and insulin-immunohistological staining of the resected pancreas (A;  $\times 100$ , B;  $\times 400$ ).

**Table 4.** Clinical course

Daily profile		Supplementary diet 2 unit v.d.s + Voglibose 0.6 mg before meal				Diazoxide 350 mg + Voglibose 0.3 mg before meal			
Time	20:30	23:00	1:00	3:00		20:30	23:00	1:00	3:00
PG (mg/dl)	114	79	57	50	⇒	192	128	97	78
IRI (mU/ml)	–	16.9	37.3	14.0		20.7	13.4	13.2	11.7
Blood pressure	140/78 mmHg				⇒	120/72 mmHg			
Urine CPR	83.2 mg/day (pre-operation)	⇒	86.0 mg/day (post-operation)	⇒	77.2 mg/day (post-operation and medication)				
75g OGTT (Diazoxide 350 mg)									
Time (min)	0	30	60	120	180				
PG (mg/dl)	66	143	183	211	185				
IRI (mU/ml)	9.7	39.3	43.3	35.8	23.9				

## Discussion

The clinical presentation of adult patients with nesidioblastosis is heterogeneous. It includes negative 72-h fasting tests in patients with noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) and is different from patients with insulinoma and also from neonates with persistent hyperinsulinemic hypoglycemia [9, 10–12]. The histological features of nesidioblastosis in adults include the presence of islet cell hypertrophy, beta cells budding off ductular epithelium, and islets in apposition to ducts [10, 13, 14]. Persons with the dumping syndrome as a result of previous gastric surgery have been reported to have increased levels of glucagon-like peptide 1 [15]. Glucagon-like peptide 1 increases beta-cell mass in rodents through neogenesis and proliferation [16]. It is possible that islet hyperfunction, especially nesidioblastosis, does not lead to obesity but that beta-cell trophic factors may increase as a result of gastric bypass [17].

The therapeutic strategies in nesidioblastosis include pancreatectomy and medical treatment with diazoxide, octreotide and corticosteroids. The initial treatment consists of nutritional management with administration of adequate amounts of calories along with the use of diazoxide. Nesidioblastosis is an uncommon but clinically important cause of hypoglycemia in the adult population, and must always be considered in patients with a presumptive preoperative diagnosis of insulinoma. Witteles *et al.* [18] reported that 70% distal

pancreatectomy often results in successful control of hypoglycemia, and rarely results in diabetes mellitus. However, they also reported that 23% of their patients showed persistent hypoglycemia with 60–89% pancreatectomy. Thus, the optimal treatment of adult-onset nesidioblastosis requires further study.

On the other hand, several medications are available for treatment of hypoglycemia. Octreotide is a somatostatin analogue used for the treatment of endocrine tumors principally to suppress hormone release and inhibit tumor growth hormone-secreting tumors [19]. The beneficial effects of octreotide are recognized in acromegaly caused by pituitary adenomas [20], chronic headache associated with pituitary gigantism [21], pancreatic islet-cell tumors and carcinoid tumors [22]. Unfortunately, it was not useful in this case.

The beta cell sulfonylurea receptor 1 [SUR1] and K<sup>+</sup> channel pore protein [Kir6.2] cluster at 11p15.1 with the Kir6.2 immediately at 3' of the SUR1 gene at ~4.5 kbp distance [4]. Recent studies have shown that impaired beta cell K<sub>ATP</sub> channel function due to mutations of the SUR1 or Kir6.2 gene is responsible for nesidioblastosis [23]. In addition to the loss of function mutation of these two proteins, gain of function mutations of glucokinase and glutamate dehydrogenase have been reported [24], and the loss of function mutation of short-chain L-3-hydroxyacyl-CoA dehydrogenase is reported to cause hyperinsulinemic hypoglycemia in human [25, 26].

In nesidioblastosis, there is some evidence to suggest the presence of dysfunctional ATP-sensitive K<sup>+</sup> chan-

nels, which are composed of  $\beta$  cell SUR1 and Kir6.2 [4, 5]. These channels initiate depolarization of  $\beta$  cell membrane and opening of  $\text{Ca}^{2+}$  channels. The resultant increases in intracellular  $\text{Ca}^{2+}$  triggers insulin secretion [6]. The mutations that cause a total loss of ATP-sensitive  $\text{K}^+$  channel in the surface membrane produce severe hyperinsulinemia of infants (HI), whereas those that impair channel function only partially produce a milder phenotype that can be treated with diazoxide or results in leucine-sensitive HI [27]. Diazoxide inhibits insulin release by opening the ATP-sensitive  $\text{K}^+$  channels, which causes hyperpolarization of the  $\beta$ -cell membrane, reduced opening of voltage-dependent  $\text{Ca}^{2+}$  channels, and eventually elimination of  $\text{Ca}^{2+}$  influx [24, 28].

Diazoxide is indicated for hypoglycemia due to hyperinsulinemia caused by inoperable pancreatic tumor, such as Langerhans hypertrophy and nesidioblastosis. It is also reported that the side-effects of such treatment are  $\text{K}^+$  and water retention, hyperglycemia and uremia [29, 30]. Although edema and weight increase were noted in our patient, these side effects improved fol-

lowing dose reduction.

Nesidioblastosis is rare in adulthood, but a few cases have been reported in Japan, especially with regard to the treatment options. In our patient, insulin hypersecretion and nocturnal hypoglycemia continued after the operation. Several recent reports indicated that not only diet therapy but also somatostatin analogue is effective against reactive hypoglycemia [30]. In our case, diazoxide treatment combined with voglibose before dinner resulted in the disappearance of nighttime hypoglycemia and the side effects. Thus, the use of diazoxide resulted in the suppression of refractory hypoglycemia and recovery of quality of life. As some patients with nesidioblastosis suffer from diabetes in the later course, we should carefully follow up the future risk of developing diabetes in patients who have diabetic family history.

In conclusion, we experienced a rare case of adult-onset nesidioblastosis. The implemented treatment strategy suggests that diazoxide may be effective for nesidioblastosis in adults and useful for the treatment of inoperable patients.

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