J Gastroenterol 1998; 33:761–765

Journal of Gastroenterology

Case report

Acinar cell carcinoma of the pancreas associated with hypoglycemia: Involvement of "big" insulin-like growth factor-II

Yohei Mizuta[1], Hajime Isomoto[1], Yoji Futuki[1], Naomi Ehara[1], Fuminao Takeshima[1], Katsuhisa Omagari[1], Kunihiko Murase[1], Yuichi Yakata[2], Masahiro Senjyu[2], Jyun-ichi Masuda[3], Nobuhiro Ikuno[3], Masuho Haraguchi[3], Keisuke Iwasaki[4], Isao Shimokawa[5], and Shigeru Kohno[1]

[1]The Second Department of Internal Medicine, and [5]The First Department of Pathology, Nagasaki University School of Medicine, 1-7-1 Sakamoto, Nagasaki 852-8501, Japan
[2]Department of Internal Medicine, Sasebo Senjyu Hospital, Sasebo, Japan
[3]Departments of Internal Medicine, [4]Pathology, Sasebo Municipal General Hospital, Sasebo, Japan

Abstract: Apart from insulinomas, pancreatic tumors are rarely complicated by hypoglycemia and some may produce insulin-like growth factor II (IGF-II). To our knowledge, IGF-II-producing pancreatic tumors associated with hypoglycemia have not been reported previously. We describe what we believe to be the first case of "big" IGF-II-producing pancreatic acinar cell carcinoma. A 68-year-old man presented with a history of recurrent hypoglycemia. Abdominal computed tomography scan and magnetic resonance imaging showed a mass, approximately 5 cm in diameter, in the tail of the pancreas and two low-density areas in the liver. Low serum glucose was associated with low insulin levels and high levels of hormones (i.e., glucagon and IGF-II) that are functionally opposite to insulin. Although serum IGF-II level was within the normal range, most IGF-II was of the high molecular weight form, as determined by Western immunoblot analysis. Based on these findings, a diagnosis of hypoglycemia induced by IGF-II-producing pancreatic tumor was made. Surgery was not possible because of the patient's poor general condition. The patient ultimately died as a result of malignant cachexia. At autopsy, a yellowish-white tumor was found in the tail of the pancreas, and a histopathologic diagnosis of acinar cell carcinoma was made. Immunohistologically, the tumor cells contained IGF-II in an irregular staining pattern, suggesting that the hypoglycemia was caused by a pancreatic tumor producing "big" IGF-II.

Key words: acinar cell carcinoma, carcinoma of the pancreas, hypoglycemia, insulin-like growth factor II

Offprint requests to: Y. Mizuta
Received Dec. 17, 1997; accepted Mar. 17, 1998

Introduction

Non-islet cell tumor associated with hypoglycemia (NICTH) is one of the major causes of hypoglycemia, and "big" insulin-like growth factor (IGF)-II produced and secreted by tumor cells is thought to be a hypoglycemic agent. Most NICTHs are mesenchymal or epithelial in origin, e.g., leiomyosarcoma, fibrosarcoma, hemangiopericytoma, mesothelioma, and hepatoma. To our knowledge, IGF-II-producing pancreatic acinar cell carcinoma has not been reported to date. We describe a case of recurrent hypoglycemia caused by acinar cell carcinoma of the pancreas producing "big" IGF-II.

Case report

A 68-year-old man, admitted to a local hospital because of repeated episodes of delirium, was found to be hypoglycemic (blood glucose 26 mg/dl). He was transferred to Nagasaki University Hospital in May 1996 for further management. On admission, he was alert, and neurological examination results were unremarkable. Mild anemia and diffuse swelling, with erythema, were noted on the dorsal region of the right hand. On abdominal examination, there was no palpable mass or localized tenderness. The remainder of the physical examination was normal. Pertinent laboratory results are shown in Tables 1 and 2. Serum glucose was 43 mg/dl and insulin was below the detection limit of the assay. The responses of immunoreactive insulin (IRI) and immunoreactive glucagon (IRG) to 75-g glucose tolerance were low and high, respectively. Abdomimal computed tomography (CT) scan (Fig. 1) and magnetic resonance imaging (MRI) demonstrated a mass with partial enhancement effect, approximately 5 cm in diameter, in the tail of the pancreas. In addition, two low-density areas in the liver, diffuse thickness of the

Table 1. Laboratory data on admission

Urinalysis		Biochemistry	
Protein	(+)	TP	7.0 g/dl
Sugar	(−)	alb	42.9%
Hematology		γ-gl	30.3%
RBC	351 × 10^4/mm^3	T.Bil	1.0 mg/dl
Hb	10.6 g/dl	GOT	19 U/l
Ht	31.4%	GPT	9 U/l
WBC	11 900/mm^3	ALP	308 U/l
St	1%	LAP	92 U/l
Seg	58%	LDH	607 U/l
Eo	4%	CPK	47 U/l
Lym	25%	Ch-E	0.40 ΔPH/h
Mo	12%	BUN	21 mg/dl
Plt	23.7 × 10^4/mm^3	CRE	1.8 mg/dl
ESR	113 mm/h	Na	135 mEq/l
Serology		K	4.0 mEq/l
CRP	3.04 mg/dl	Cl	100 mEq/l
FBS	43 mg/dl	AMY(S)	294 IU/l
Tumor markers		Trypsin	190 000 ng/ml
CEA	2.7 ng/ml	Lipase	3560 U/l
CA 19-9	97.9 U/ml	PLA2	48 000 ng/dl
Elastase-1	7250 ng/dl	Feces	
SPAN-1	49.3 U/ml	Occult blood	(+)
DUPAN-2	178 U/ml		
AFP	396.0 ng/ml		

Table 2. Endocrinological examination

75 g OGTT	BS (mg/dl)	IRI (μU/ml)	IRG (pg/ml)
Before	53	[a]	587
30 min	65	[a]	586
60 min	80	0.6	533
90 min	89	1.5	577
120 min	108	2.9	595

hGH	2.2 ng/ml	Gastrin	14 pg/ml
Cortisol	16.0 μg/dl	Secretin	244 pg/ml
$FreeT_4$	1.3 ng/dl	VIP	23 pg/ml
TSH	1.84 μU/ml	IGF-I	<11 ng/ml
C-peptide	0.4 ng/ml	IGF-II	533 ng/ml
Anti insulin Ab	7%	IGFBP-3	3.68 μg/ml

[a] Below detection limit of assay; BS, Blood sugar; IRI, immunoreactive insulin; IRG, immunoreactive glucagon

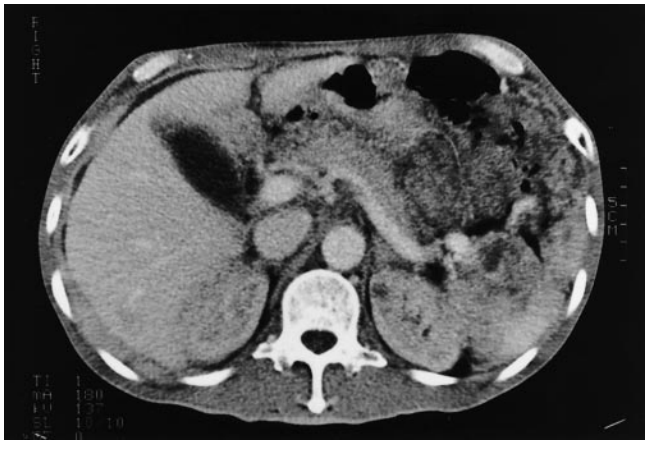

Fig. 1. Abdominal CE computed tomography scan showing a well-defined mass with a few low-density areas in the tail of the pancreas

peritoneum, and a high density of mesenteric fat were present. Endoscopic examination of the upper gastrointestinal tract showed erosive duodenitis, and histological examination of a biopsy specimen obtained from that region showed no malignancy. Endoscopic retrograde pancreatography (ERP) showed interruption of the main pancreatic duct (Fig. 2). Angiography was not performed.

Based on these clinical, investigative, and laboratory findings, a provisional diagnosis of pancreatic tumor with liver metastasis and carcinomatous peritonitis was made. The condition was most likely the underlying cause of the hypoglycemia. Because of the low insulin level and high or normal levels of hormones that are functionally opposite to insulin (i.e., glucagon and IGF-II), we extended our laboratory investigation by examining the level of IGF (Table 2). The concentration of somatomedin-C (IGF-I) was below 11 ng/ml (normal range, 88–240 ng/ml), while the level of IGF-binding protein-3 was 3.68 μg/ml. Although serum levels of IGF-II were within the normal range (533 ng/ml), most IGF-

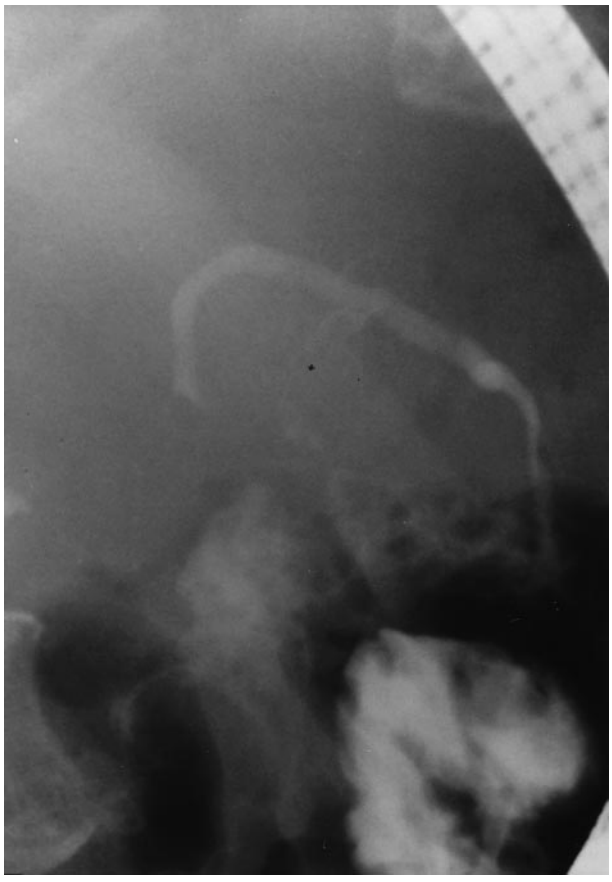

Fig. 2. Endoscopic retrograde pancreatography showing interruption of the main pancreatic duct in the tail of the pancreas

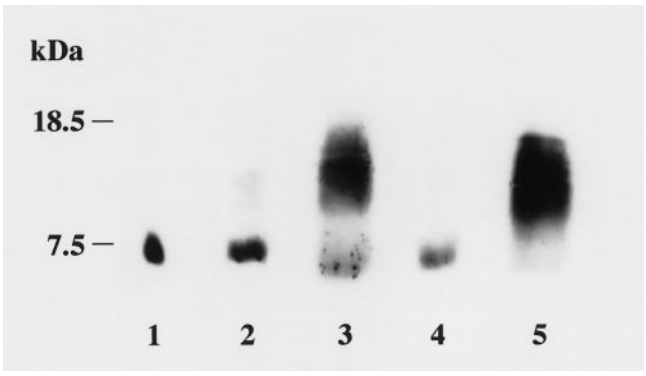

Fig. 3. Western immunoblot analysis of serum insulin-like growth factor (IGF)-II. Recombinant human IGF-II and authentic IGF-II in normal adult are shown in *lanes 1 and 2*, respectively. A high molecular weight form of IGF-II in a patient with non-islet cell tumor associated with hypoglycemia (NICTH) and IGF-II in a patient with hypoglycemia of unknown origin are shown in *lanes 3 and 4*, respectively. Most IGF-II in the present patient with NICTH, *shown in lane 5*, is present in the 11 to 18-kDa fraction, similar to that shown in *lane 3*

II consisted of a high-molecular weight form (11 to 18-kDa fraction) by Western immunoblot analysis using mouse anti-IGF-II monoclonal antibody (Amano Pharmaceutical, Nagoya, Japan) (Fig. 3). Based on these results, we made a provisional disagnosis of IGF-II-producing pancreatic tumor, causing hypoglycemia.

While the patient was hospitalized, intravenous hyperalimentation was provided. However, his general condition, and, in particular, his renal function, deteriorated gradually, and intensive anti-neoplastic chemotherapy was not used. At the patient's request, he was transferred to a nearby hospital. He died of malignant cachexia on August 3, 1996.

At autopsy, a yellowish white tumor, 60 × 40 × 40 mm in size, was found in the tail of the pancreas. The cut surface showed a well circumscribed, lobulated nodule with necrotic foci. Numerous nodules, ranging from 2 to 10 mm in diameter, were noted on the surface of the peritoneum and mesentery, resembling carcinomatous peritonitis, and there was blood-stained ascites (1200 ml). A metastatic focus, 10 mm in diameter, was also found in the liver. Light microscopic examination showed round neoplastic cells arranged in an acinar pattern with small lumina and with solid growth frequently intermingled (Fig. 4). The neoplastic cells contained abundant granular cytoplasm. These granules were Periodic acid-Schiff-positive but diastase-resistant, as shown by histochemistry. Immunohistochemical analysis showed only a few cells positive for neuroendocrine markers such as chromogranin A or synaptophysin, while most cells were immunoreactive for anti-trypsin and anti-alpha chymotrypsin. Based on the growth pattern of the neoplastic cells, a pathologic diagnosis of pancreatic acinar cell carcinoma was established. Immunohistological examination using a mouse anti-IGF-II monoclonal antibody (Amano Pharmaceutical) demonstrated that both the pancreatic tumor and the metastatic liver tumor contained IGF-II, which showed an irregular staining pattern (Fig. 5).

Discussion

Since the first report by Daughaday et al.[1] showing high serum IGF-II levels in patients with NICTH, it is now clear that IGF-II produced and secreted by the tumor causes hypoglycemia. However, the serum concentration of IGF-II is not always elevated in these patients. In 1988, Daughaday et al.[2] reported a high percentage of the high molecular weight form of IGF-II in NICTH, suggesting that heterogenous IGF-II may be related to hypoglycemia.

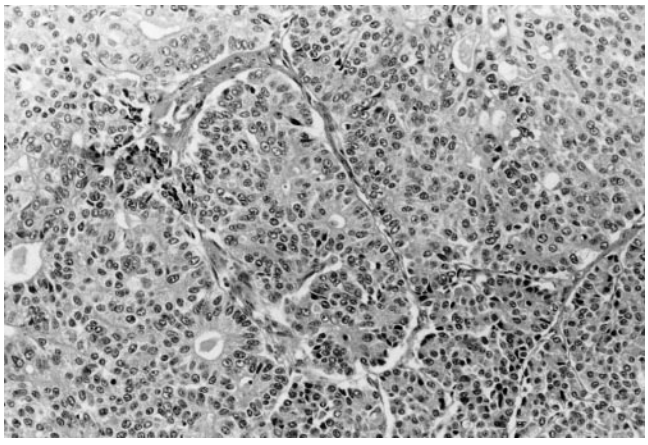

Fig. 4. Light microscopic examination of the pancreatic tumor, showing neoplastic cell growth in an acinar pattern with small lumina and frequently intermingled solid growth. H&E, ×100

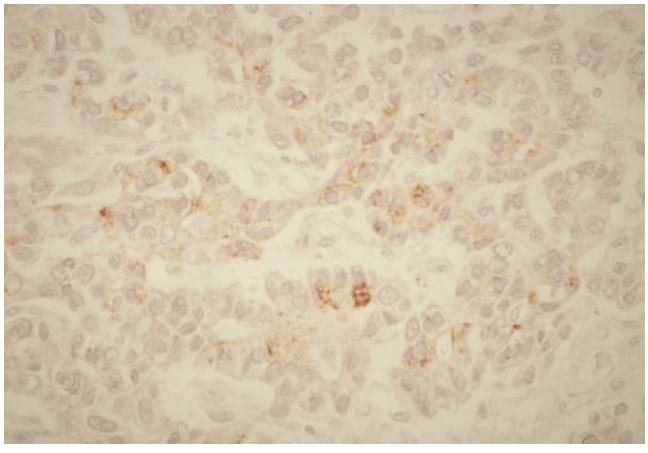

Fig. 5. The cytoplasm of neoplastic cells from pancreatic tumor was positive for IGF-II. ABC method, ×200

Most NICTHs are either mesenchymal or epithelial in origin; e.g., leiomyosarcoma, fibrosarcoma, hemangiopericytoma, mesothelioma, and hepatoma. In regard to pancreatic exocrine tumors, we have found only one reported case of disseminated pancreatic carcinoma of ductal type accompanied by spontaneous hypoglycemia; hormonal analysis showed negligible insulin concentrations, but raised IGF-II levels together with low IGF-I concentrations.[3] To our knowledge, our patient represents the first documented case of hypoglycemia associated with pancreatic acinar cell carcinoma producing IGF-II. His clinical features of hypoglycemia, low serum IRI, and low serum IGF-I level allowed the diagnosis of NICTH. Although his serum IGF-II level was not elevated, the IGF-II/IGF-I ratio was more than 48. Fukuda et al.[4] suggested that the presence of inappropriately low levels of IGF-I in relation to IGF-II was characteristic of IGF-II-producing NICTH. Further, most IGF-II was "big" IGF-II, with a higher molecular weight relative to authentic IGF-II.[2,4] In our patient, most IGF-II was of high molecular weight, 11–18 kDa. It is thought that "big" IGF-II develops because of defective processing caused by tumors.[5] Under normal conditions, IGF-II is produced in the liver, and circulating IGF-II is present in a tertiary 150-kDa complex composed of IGF-II, IGF binding protein (IGFBP)-3, and an acid labile subunit. Because IGF-II does not interact with insulin receptors, hypoglycemia does not occur. However, "big" IGF-II fails to form this complete complex.[6] Although the mechanism of "big" IGF-II-induced hypoglycemia is not clear, increased consumption of glucose through insulin receptors is suggested,[2] and high levels of free IGF-II[7,8] and increased bioactivity caused by changes in IGFBP[9,10] may be important.

Our patient had frequent episodes of hypoglycemia-induced states of delirium, and a complete laboratory and radiologic investigation showed a pancreatic tumor that was not an insulinoma. Although a provisional diagnosis of IGF-II-producing pancreatic tumor was made, based on the serum level of IGF and Western immunoblot analysis of IGF-II, a definitive diagnosis of acinar cell carcinoma was not established. At autopsy, the pancreatic acinar cell carcinoma with liver metastasis contained IGF-II in an irregular staining pattern, confirming the diagnosis and suggesting that hypoglycemia was related to the "big" IGF-II-producing tumor.[10] The incidence of acinar cell carcinoma among pancreatic carcinomas is about 1%.[11] Complications of polyarthropathy[12] and subcutaneous fat necrosis,[13] which may be related to lipase or phospholipase A_2, have been reported. It is possible that the erythematous swelling on the right hand in our patient was caused by the high levels of lipase and phospholipase A_2 produced by the tumor.

Some cases of IGF-II-producing gastrointestinal carcinomas, such as gastric cancer[14] or rectal cancer[15] have been reported, and most of these patients had liver metastasis. Likewise, our patient with pancreatic acinar cell carcinoma had liver metastasis. Although it is not certain why NICTH of the digestive system is often accompanied by liver metastasis, the increased tumor cell mass or direct drainage of "big" IGF-II to the systemic circulation, in association with liver metastasis, may be important for the induction of hypoglycemia.

Previous studies have shown the effectiveness of various treatments for NICTH associated with IGF-II. Surgical removal of the tumor or radiotherapy reduces the excess IGF-II, thereby ameliorating the hypoglycemia.[16–18] Hunter et al.[19] reported the beneficial effects

of growth hormone and intrahepatic adriamycin in IGF-II-producing hepatomas. In our patient, intensive therapy was not possible because of his poor general condition.

In conclusion, it is important to recognize that acinar cell carcinoma of the pancreas may cause severe hypoglycemia because of the production and secretion of "big" IGF-II.

Acknowledgments. We are grateful to Dr. Naomi Hizuka, Department of Medicine, Institute of Clinical Endocrinology, Tokyo Women's Medical College, for the Western immunoblot analysis of serum IGF-II and to Dr. Motohiko Aiba, Department of Pathology, Second Hospital, Tokyo Women's Medical College, for the immunohistological examination of IGF-II.

References

1. Daughaday WH, Trivedi B, Kapasia M. Measurement of insulin-like growth factor II by a specific radioreceptor assay in serum of normal individuals, patients with abnormal growth hormone secretion, and patients with tumor associated hypoglycemia. J Clin Endocrinol Metab 1981;53:289–294.
2. Daughaday WH, Emanuele MA, Brooks MH, et al. Synthesis and secretion of insulin-like growth factor II by a leiomyosarcoma with associated hypoglycemia. N Engl J Med 1988;319:1434–1440.
3. Sturrock NDC, Selby C, Hosking DJ. Spontaneous hypoglycaemia in a non-insulin-dependent diabetes mellitus patient with disseminated pancreatic carcinoma. Diabet Med 1997;14:324–326.
4. Fukuda I, Hizuka N, Takano K, et al. Characterization of insulin-like growth factor II (IGF-II) and IGF binding proteins in patients with non-islet-cell tumor hypoglycemia. Endocrine J 1993;40:111–119.
5. Daughaday WH. Autocrine, paracrine and endocrine manifestations of insulin-like growth factor secretion by tumors. In: Spencer EM (ed) Modern concepts of insulin-like growth factors. New York: Elsevier, 1991;557.
6. Daughaday WH, Kapadia M. Significance of abnormal serum binding of insulin like growth factor II in the development of hypoglycemia in patients with non-islet-cell tumors. Proc Natl Acad Sci USA 1986;86:6778–6782.
7. Shapiro ET, Bell GI, Polonsky KS, et al. Tumor hypoglycemia: Relationship to high molecular weight insulin-like growth factor II. J Clin Invest 1990;85:1672–1679.
8. Fukuda I, Hizuka N, Takano K, et al. Circulating forms of insulin-like growth factor II (IGF-II) in patients with non-islet cell tumor hypoglycemia. Endocrinol Metab 1994;1:89–95.
9. Zapf J, Futo E, Peter M, et al. Can big insulin-like growth factor II in serum of tumor patients account for the development of extrapancreatic tumor hypoglycemia? J Clin Invest 1992;90:2574–2584.
10. Wasada T, Hizuka N, Yamamoto M, et al. An insulin-like growth factor II-producing histiocytoma associated with hypoglycemia: Analysis of the peptide, its gene expression, and glucose-transporter isoforms. Metabolism 1992;41:310–316.
11. Cubilla AC, Fitzgerald PJ. Tumors of the exocrine pancreas, Washington DC: Armed Forces Institute of Pathology, 1984;208–212.
12. Burns WA, Matthews MJ, Hamosh M, et al. Lipase-secreting acinar cell carcinoma of the pancreas with polyarthropathy. Cancer 1974;33:1002–1009.
13. Radin DR, Colletti PM, Forrester DM, et al. Pancreatic acinar cell carcinoma with subcutaneous and intraosseous fat necrosis. Radiology 1986;158:67–68.
14. Horiuchi T, Shinohara Y, Sakamoto Y, et al. Expression of insulin-like growth factor II by a gastric carcinoma associated with hypoglycaemia. Virchows Arch 1994;424:449–452.
15. Merimee TJ. Insulin-like growth factors in patients with nonislet cell tumors and hypoglycemia. Metabolism 1986;35:360–363.
16. Baxter RC, Daughaday WH. Impaired formation of the ternary insulin-like growth factor-binding protein complex in patients with hypoglycemia due to nonislet cell tumors. J Clin Endocrinol Metab 1991;73:696–702.
17. Eastman RC, Carson RE, Orloff DG, et al. Glucose utilization in a patient with hepatoma and hypoglycemia: Assessment by positron emission tomography. J Clin Invest 1992;89:1958–1963.
18. Zapf J. Role of insulin-like growth factor (IGF) II and IGF binding proteins in extrapancreatic tumour hypoglycemia. J Intern Med 1993;234:543–552.
19. Hunter SJ, Daughaday WH, Callender ME, et al. A case of hepatoma associated with hypoglycemia and overproduction of IGF-II (E-21): Beneficial effects of treatment with growth hormone and intrahepatic adriamycin. Clin Endocrinol 1994;41:397–401.