The Korean Journal of Internal Medicine: 18:45-49, 2003

A Large Malignant Insulinoma : Case Report with Endosonographic, Immunohistochemical and Ultrastructural Features

Chang Hwa Lee, M.D., Goo Lee, M.D., Dong Hoon Kim, M.D.*,
Nam Il Kim, M.D., Sung Ja Kim, M.D., Chang Woo Lee, M.D.
and Kuk Hyun Song, M.D.†

Departments of Internal Medicine and Pathology, College of Medicine, Dongguk University, Gyeongju, Korea;*
Department of General Surgery†, Sunlin Hospital, Handong University, Pohang, Korea

Malignant insulinoma in the beta cells of the pancreatic islet is rare and usually presented as hypoglycemia. We report a case of large malignant insulinoma in a 53-year-old Korean woman. A presumptive clinical diagnosis was made before surgery, based on the high plasma insulin-to-glucose ratio and a large solitary heterogeneous pancreatic mass by abdominal computed tomography and endosonography. The tumor measured 5.8×4.7×4.5 cm in dimension and showed capsular invasions and metastases in two of four peripancreatic lymph nodes. The tumor cells were strongly immunoreactive to insulin and had a high Ki-67 labeling index (13%) and atypical membranous electron-dense granules, ranging from 120 to 400 nm in diameter, in the cytoplasm on electron microscopy. The patient was treated by distal pancreatectomy with splenectomy and rapidly recovered without neurohypoglycemic symptoms. This case showed not only lymph node metastases, the most reliable parameter for malignancy in pancreatic endocrine tumors, but also other valid diagnostic clues, such as high Ki-67 labeling index, heterogeneous enodosonographic findings, capsular invasions with large tumor and pure atypical secretory granules.

Key Words: Hypoglycemia; Carcinoma, Islet Cell; Endosonography; Microscopy, Electron; Ki-67 Antigen

INTRODUCTION

Insulinomas are uncommon endocrine tumors arising from the pancreatic β cells. Most insulinomas are benign, single and small, measuring less than 2 cm in diameter. Only 8% were greater than 5 cm[1-5]. Malignant insulinomas are rare and few cases have been reported in Korea[2, 6-9]. Differentiation between benign and malignant insulinomas by histologic finding was difficult, therefore malignant insulinomas were diagnosed only by metastasis to lymph nodes or other organs[3, 5]. Hence we report a patient of a large malignant insulinoma with peripancreatic lymph node metastases and characterize it's endosonographic, immunohistochemical and electron microscopic features.

CASE

A 53-year-old woman presented with recurrent dizziness and loss of consciousness upon skipping meals for several months. She was known as a 'shaman' in her neighborhood because of frequent faintness. On admission, the results of complete blood counts, tumor markers, thyroid function test, parathyroid hormone, calcium, gastrin, prolactin and brain

• Received : October 31, 2002.
• Accepted : January 4, 2003.
• Correspondence to : Goo Lee, M.D., Department of Internal Medicine, Dongguk University Hospital, 646-1, Jukdo-2-dong, Pohang 791-050, Korea.
E-mail : leegoo2@chollian.net

computed tomography (CT) were normal, but the random glucose level was 39 mg/dL. On 72-hour fasting test, she demonstrated cold sweat, disorientation, and dizziness at 5 hours with 25 mg/dL of serum glucose level. The plasma insulin-to-glucose ratio was 1.41 (Table 1) and symptoms were immediately relieved following glucose administration (Figure 1). Preoperative localization was done by abdominal CT and endosonography (EUS). A hypoechoic, heterogeneous echoic mass was discovered at the tail of the pancreas (Figure 2, 3). Distal pancreatectomy with splenectomy was done.

Table 1. Serum levels of fasting insulin, glucose and C-peptide

	admission	post-operation†	Follow-up‡
Insulin (μu/mL)	38.10	22.30	17.40
Glucose (mg/dL)	25	98	104
I/G ratio (U/mL/mg/dL)*	1.41	0.22	0.16
C-peptide (ng/mL)	6.7	4.3	3.9

* I/G ratio, insulin/glucose ratio
† 1 day after post-operation
‡ Follow-up after 6 months

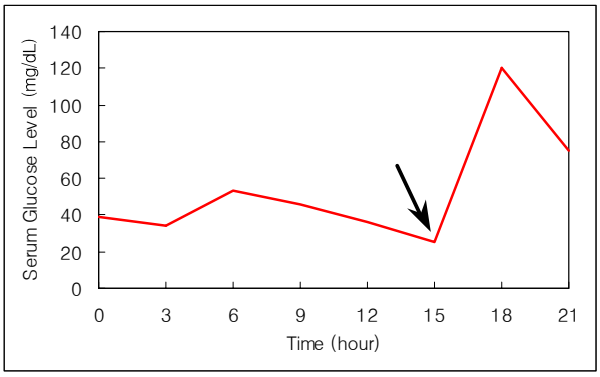

Figure 1. Measurement of serum glucose on 72-hour fasting test. The arrow indicates the time-point of glucose administration

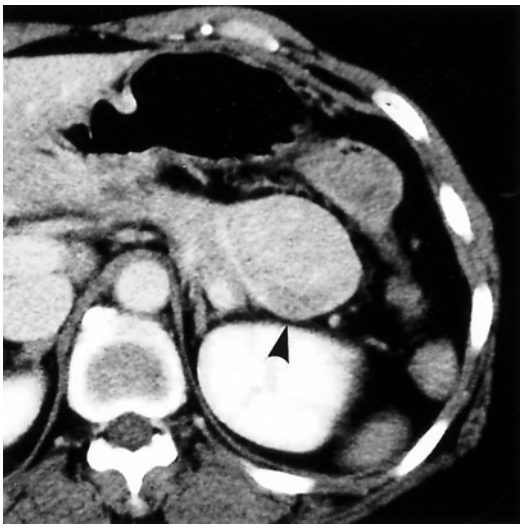

Figure 2. Abdominal CT showed a single, round, well-enhanced mass in the tail of the pancreas, measuring 6 cm in diameter. Neither lymph node enlargement nor metastatic lesion was visible.

The mass measuring 5.8×4.7×4.5 cm in dimension (Figure 4) was composed of uniform bland cuboidal cells with granular eosinophilic cytoplasm and round nuclei (Figure 5A). Two of four peripancreatic lymph nodes were metastasized (Figure 5B). Immunohistochemically, cytoplasm of tumor cells were strongly immunoreactive to insulin (Figure 6A) but not to somatostatin and glucagon. The Ki-67 labeling index (LI) was approximately 13% (Figure 6B). On ultrastructural study, atypical secretory granules were easily found in the cytoplasm (Figure 7A). Amyloid deposits were showed both by electron microscopy (EM, Figure 7B) and congo red stain under polarizing microscopy (Figure 8). Immediate after surgery, the levels of insulin and glucose were normalized and the postoperative course was uneventful and without any complication (Table 1). During 18-months of follow-up, she remains with no evidence of recurrence.

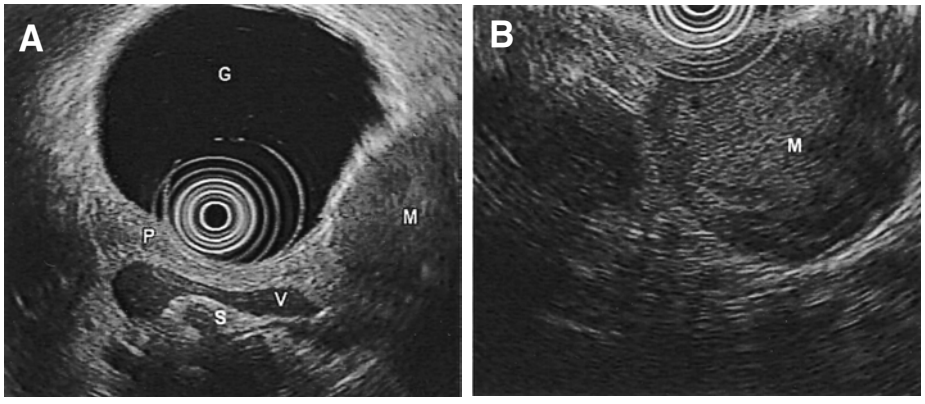

Figure 3. Hypoechoic, heterogeneous with multiple anechoic spots and a smooth delineation without other intra-pancreatic occult mass were detected by EUS at a frequency of 7.5 MHz (G: stomach, M: mass, P: pancreas, S: superior mesenteric artery, V: splenic vein).

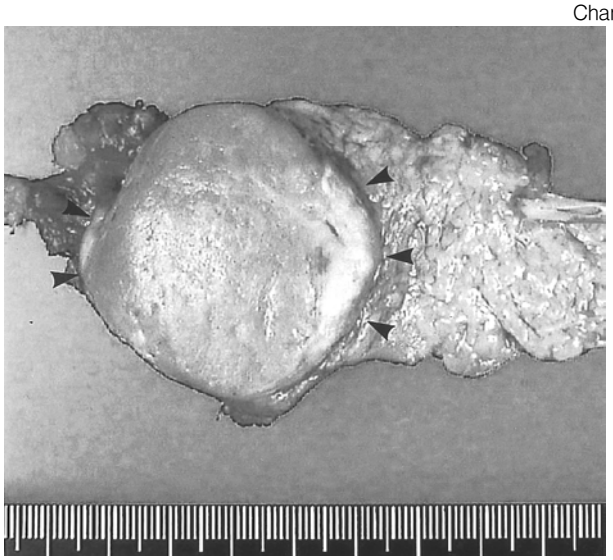

Figure 4. The tumor mass was oval, well-demarcated solid, measuring 5.8×4.7×4.5 cm in dimension. Two foci of capsular invasion (arrowheads) were observed in the cut surface.

DISCUSSION

Insulinomas are the most common pancreatic endocrine tumors (PETs) and only less than 10% are malignant. Malignant insulinoma could be suspected clinically if the size of the tumor is 3 to 6 cm or larger and confirmed bythe evidence of metastasis which is mostly found in the liver, lymph nodes, or both[1-4].

A large variety of imaging modalities for the preoperative localization have been used, but the average accuracy remains low[5, 10, 12, 19]. Recently, EUS is a new convenient diagnostic method for the localization of a pancreatic mass[10-14]. The sensitivity and specificity of EUS are up to 82~93% and 95%, respectively[10-12].

Differentiations between benign and malignant insulinoma by EUS depend upon size, heterogeneity of internal echo, multinodular structure, cystic transformation or necrosis and vascular invasion[11]. In our case EUS findings that demonstrated large-sized, low-echoic mass with heterogeneous

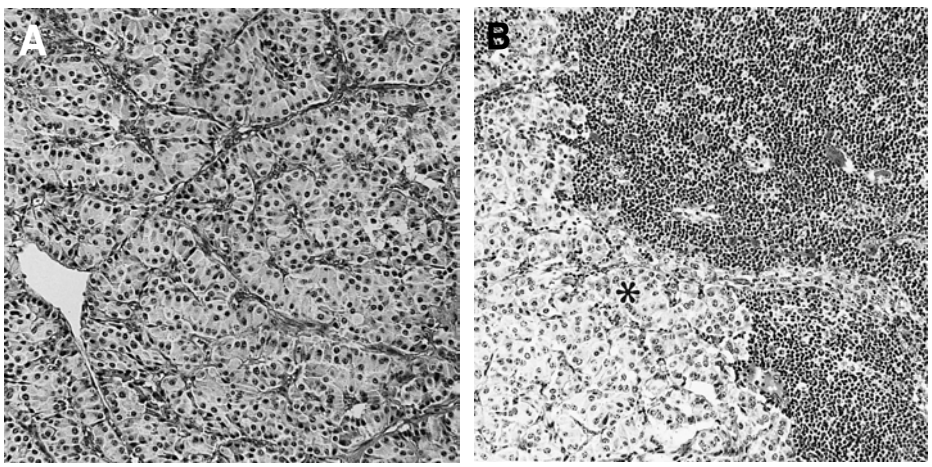

Figure 5. The tumor demonstrated small nests of uniform bland cells septated by thin fibrovascular stroma (A). A peripancreatic lymph node was metastasized by tumor cells (asterisk) (B), (H&E, ×100).

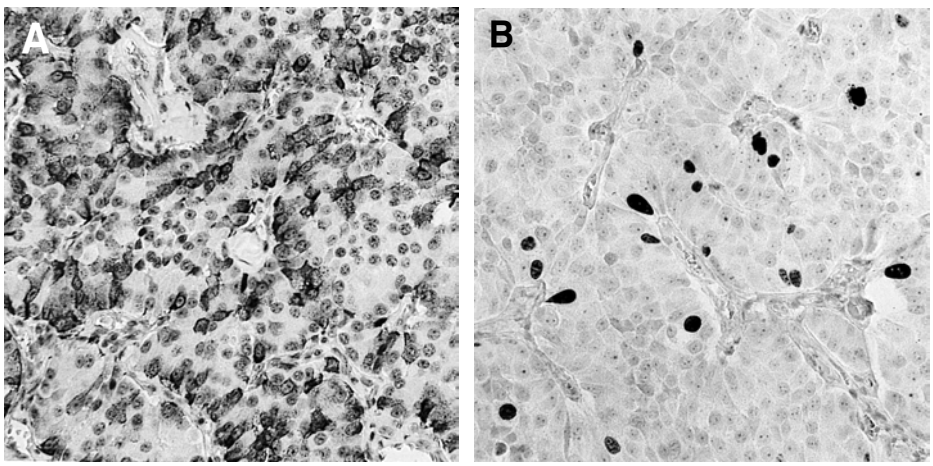

Figure 6. The cytoplasm of the tumor cells was strongly immunoreactive (dark-brown) for the insulin (A). A few tumor nuclei showed immunoreactive (dark-brown) for Ki-67 (B), (×200).

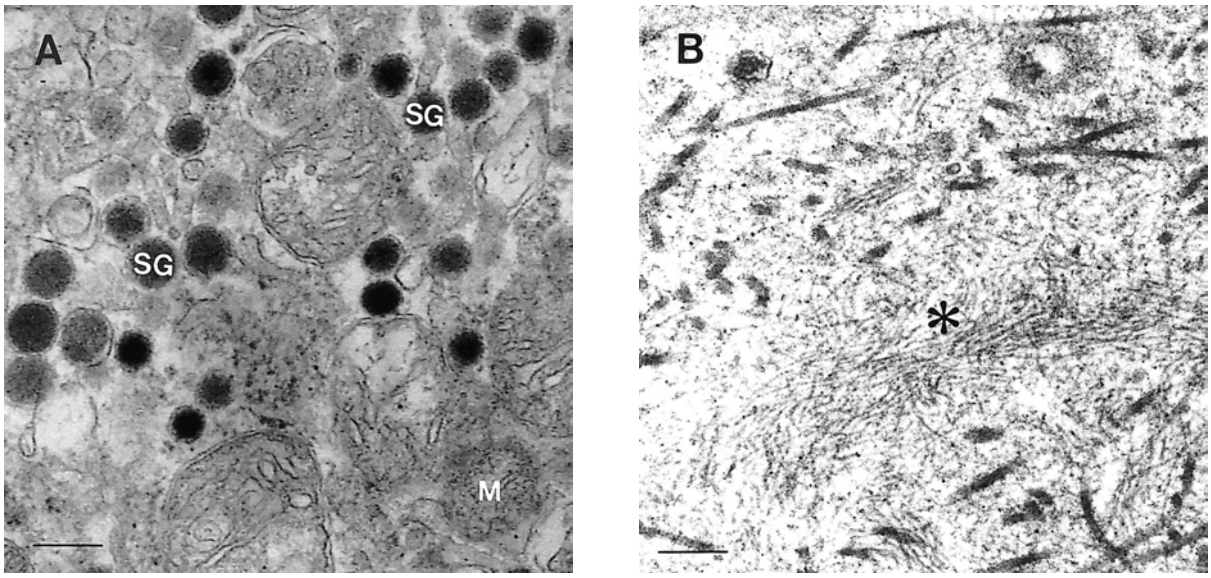

Figure 7. EM demonstrated well-developed, membranous, electron-dense atypical secretory granules (SG) in the cytoplasm measuring 120 to 400 nm (A). There were wisps of non-branching intermediate amyloid filaments (asterisk) in the extracellular spaces (B). (M: mitochondria. Scale bar: 0.5 μm).

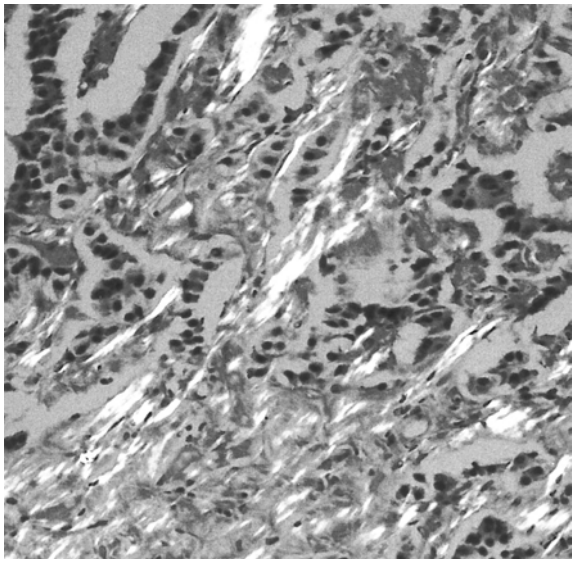

Figure 8. Amyloid deposits near the vessels were exhibited yellow-green birefringence under polarizing microscopy (Congo red stain, × 200).

internal echo evoked a possibility of malignancy. The Ki-67 LI is known to be less than 5% in benign tumors, but it was estimated as 13% in this tumor which could be a predictable feature of a malignant tumor[15].

More than half of the PETs secrete multiple hormones (insulin, glucagon, somatostatin), nevertheless, the clinical manifestations are nearly always derived from hypersecretion of only one of these hormones[16]. In our case, the tumor cells were only immunoreactive to insulin, therefore, seemed to be as a pure insulinoma.

Ultrastructurally, our tumor was devoid of typical insulin-secreting β granules and only showed a decreased number of atypical secretory granules comparing with normal islet β cell. Because atypical granule could be regarded as an incomplete form in the maturation process and stored with a small amount of functional insulin, these findings might be correlated with long, insidious, endurable clinical symptoms and malignant potential. Metastasis is the most reliable parameter for malignancy in PETs. However, high LI, heterogeneous EUS findings, capsular invasion with large tumor and pure atypical secretory granules might be other valid diagnostic clues for diagnosis of malignant insulinoma. Amyloid deposits were shown under polarized light after Congo red stain and electron microscopy. Those were thought to be the result of uncontrolled insulin or proinsulin release with decreased storage capacity[17].

Insulinoma is usually managed by surgical excision, laparoscopic enucleation[14] or medical treatment. Distal pancreatectomy with splenectomy was performed because of the unfavorable EUS findings. For patients with benign insulinoma, the long-term cure rate is about 88.6～97.5% by surgical treatment[18, 19], and patients with malignant insulinoma have a 49～66% of 5-year survival[20, 21] with 7.5-year of overall survival[3]. The patient has remained well for 18 months after surgical excision of the tumor, despite some unfavorable prognostic factors such as lymph node metastases, capsular invasions and high LI.

REFERENCES

1) Stefanini P, Carboni M, Partrassi N, Basoli A. *Beta-islet cell tumors of the pancreas: results of a study of 1,067 cases. Surgery 75:597-609, 1974*
2) Cha KS, Kim J, Kim IC. *Malignant insulinoma. J Kor Surg Soc 24:305-309, 1982*
3) Danforth DN Jr, Gorden P, Brennan MF. *Metastatic insulin-secreting carcinoma of the pancreas: clinical course and the role of surgery. Surgery 96:1027-1037, 1984*
4) Brentjens R, Saltz L. *Islet cell tumors of the pancreas: The medical oncologist's perspective. Surg Clin North Am 81:527-542, 2001*
5) Norton JA, Shawker TH, Doppman JL Miller DL, Fraker DL, Cromack DT. *Localization and surgical treatment of occult insulinomas. Ann Surg 87:385-387, 1990*
6) Park DJ, Rhee BD, Yi KH, Bang YJ, Cho BY, Lee HK, Kim NK, Koh CS, Min HK. *A case of malignant insulinoma: Partial remission by combination chemotherapy of streptozotocin and 5-FU. J Kor Soc Endocrin 3:255-260, 1988*
7) Jun YC, Lim BH, Son BJ, Kim BI, Lee MH, Lee SJ. *A case of malignant insulinoma treated with streptozotocin after surgery. J Kor Soc Endocrin 9:150-155, 1994*
8) Kwon HC, Lee JI, Kang DY, Kim JS, Kim HJ, Kim DK, Kim JS. *A case of malignant insulinoma resistant to octreotide and combination chemotherapy. J Kor Soc Endocrin 10:300-305, 1995*
9) Jeong CH, Kwon YJ, Han SS, Kim JH, Lee BD, Kim KH, Moon BC. *A case of malignant insulinoma: Effect of a somatostatin analogue (SMS 201-995) on serum glucose and insulin. Kor J Int Med 41:282-288, 1991*
10) Rösch T, Lighydale CJ, Botet JF, Boyce GA, Sivak Jr MV, Yasuda K, Hyder N, Plazzo L, Doncygier H, Schusdizarra V, Classen M. *Localization of pancreatic endocrine tumors by endoscopic ultrasonography. N Eng J Med 326:1721-1726, 1992*
11) Kann P, Bittinger F, Engelbach M, Bohner S, Weis A, Beyer J. *Endosonography of insulin-secreting and clinically non-functioning neuroendocrine tumors of the pancreas: criteria for benignancy and malignancy. Eur J Med Res 28:385-390, 2001*
12) Ardenjh JC, Rosenbaum P, Ganc AJ. *Role of EUS in the preoperative localization of insulinomas compared with spiral CT. Gastrointest Endosc 51:552-555, 2000*
13) Menzel J, Domschke W. *Intraductal ultrasonography may localize islet cell tumours negative on endoscopic ultrasound. Scand J Gastroenterol 33:109-112, 1998*
14) Oh YJ, Oh JH, Kim NH, Park IB, Kim SJ, Baik SH, Choi DS, Seo SO, Kim MG. *A case of insulinoma which was treated by laparoscopic enucleation. J Kor Soc Endocrin 13:665-669, 1998*
15) Pelosi G, Bresaola ME, Bogina CG, Pasini F, Rodella S, Castelli P, Icacono C, Serio G, Zamboni G. *Endocrine tumors of the pancreas: Ki-67 immunoreactivity on paraffin section is an independent predictor for malignancy: A comparative study with proliferating-cell nuclear antigen and progesterone receptor protein immunostaining, mitotic index and other clinicopathologic variables. Hum Pathol 27:1124-1133, 1996*
16) Lam KY, Lo CY. *Pancreatic endocrine tumour: a 22-year clinicopathologic experience with morphological, immuno-histochemical observation and a review of the literature. Eur J Surg Oncol 23:36-42, 1997*
17) Creutzfeldt W. Arnold R. Creutzfeldt C. Deuticke U. Frerichs H. Track NS. *Biochemical and morphological investigations of 30 human insulinomas. Correlation between the tumour content of insulin and proinsulin-like components and the histological and ultrastructural appearance. Diabetologia. 9:217-231, 1973*
18) Grama D, Eriksson B, Martensson H, Cedermark B, Ahren B, Kristoffersson A, Rastad J, Oberg K, Akerstrom G. *Clinical characteristics, treatment and survival in patients with pancreatic tumors causing hormonal syndromes. World J surg 16:632-639, 1992*
19) Rothmund M, Angelini L, Brunt LM. *Surgery for benign insulinoma: An international review. World J Surg 14:393-398, 1990*
20) Kuzin NM, Egorov AV, Kondrashin SA, Lotov AN, Kuznetzov NS, Majorova JB. *Preoperative and intraoperative topographic diagnosis of insulinomas. World J Surg 22:593-597, 1998*
21) Phan GQ, Yeo CJ, Hruban RH, Lillemoe KD, Pitt HA, Cameron JL. *Surgical experience with pancreatic and peripancreatic neuroendocrine tumors: review of 125 patients. J Gastrointest Surg 2:472-482, 1998*