Hiroshima J. Med. Sci.
Vol. 47, No.2, 69~72, June, 1998
HIJM 47-10

Tumor Localization Studies and Surgical Treatment in Patients with Insulinoma

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ABSTRACT

In the present study, we retrospectively reviewed thirteen consecutive patients with insulinomas including 2 reoperations at our department for insulinomas, from the viewpoint of preoperative localization studies, surgery and long term follow-up. The results of the preoperative localization studies proved to be percutaneous transhepatic portal venous sampling (PTPVS) 6/7, angiography 8/15, ultrasonography (US) 6/11, endoscopic ultrasonography (EUS) 4/4, computed tomography (CT) 3/10, and magnetic resonance imaging (MRI) 2/2. The tumor was visualized by intraoperative ultrasonography (IUS) in 6 of 6 patients (100%). Six patients underwent enucleation, 6 patients underwent distal pancreatectomy, 2 patients underwent subtotal (80%) distal pancreatectomy, and one patient a pylorus preserving pancreaticoduodenectomy (PPPD). Two patients, one of whom belonged to the MEN-I group, underwent reoperations because they had multiple adenomas. The development of iatrogenic diabetes occurred in the case of 3 patients. These results suggest that the use of selected preoperative localization studies (PTPVS and probably EUS) may be very helpful for detecting insulinoma, and that IUS is an essential part of the operative exploration for insulinoma. Our data may further indicate the need for an aggressive surgical procedure in the case of multiple adenoma or insulinoma in MEN-I

Key words: *Insulinoma, Multiple endocrine neoplasia type-1*

Insulinoma is still a rare disease, although it is the most common islet cell tumor. The fascination that it holds for surgeons lies in its elegance as a model for the surgical cure of a biochemical derangement. The metabolic effects of these tumors are life-threatening, whereas the lesions themselves are usually small, benign and hidden from all but the most diligent efforts[17].

Several centers around the world have reported excellent results with respect to the management of patients with insulinomas. Surgical failures, however, do occur, primarily as a result of (1) surgical inexperience, (2) multicentric disease, (3) malignant tumors and (4) improper diagnosis.

In the present study, we retrospectively reviewed thirteen consecutive patients of insulinomas, including 2 reoperations at our department for insulinomas, from the viewpoint of preoperative localization studies, surgery and long term follow-up.

MATERIALS AND METHODS

The objectives were 13 patients (15 operations) for whom the operations were performed in our department during a 29-year period up to 1997. Their ages ranged from 29 to 79 years, and the sex ratio was 3 males and 10 females (Table 1). Preoperative and intraoperative localization studies, pathology, surgical results and follow-up were analyzed for each individual patient.

RESULTS

In all cases, the main clinical symptoms were unconsciousness, a dazed condition, asthenia and other neuropsychiatric symptoms. The first 6 cases were reported previously[9]. All but one patient (No.11) showed Whipple's triad positive at admission.

The results of preoperative localization studies are shown in Table 2. The rates of true-positive proved to be PTPVS 6/7 (86%), angiography 8/15 (53%), US 6/11 (55%), EUS 4/4 (100%), CT 3/10 (30%), and MRI 2/2 (100%). PTPVS selectively localized tumors to the correct region of the pancreas in 6 of 7 studies. In the case of patient No. 13-II, only EUS and MRI identified the recurrent

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Table 1. Patient and tumor characteristics

Patient No.	Age (year)	Gender	Size (cm)	Location	Excisional procedure	Histology	Iatrogenic. D. M.	Follow-up study
1	35	F	3.5×3×3	tail	enucleation	single adenoma	(–)	died 2 years due to duodenal perforation
2	69	M	3×2.5×1.5	tail	enucleation	single adenoma	(–)	healthy at least 12years
3	70	F	1.5×1×1	body	enucleation	single adenoma	(–)	healthy for 21 years
4	69	F	1×1×1	body	enucleation	single adenoma	(–)	died 1 year and 10 months due to hepatic failure
5	39	M	0.8×0.8	head	subtotal distal pacreatectomy	single adenoma	(–)	healthy for 16 years
6-I	58	F	1.5×1×1	head	enucleation	single adenoma	(–)	recurrence of hypoglycemic attack at 7months
6-II	58	F	0.1 to 1.7 ×1.5×1	head to tail	subtotal distal pancreatectomy	multiple adenoma	(–)	healthy for 14 years
7	52	F	1.5×1.2×1.5	body	distal panccreatectomy	single adenoma	(+)	healthy for 11 years
8	79	F	1.2×1×0.8	body	enucleation	single adenoma	(–)	healthy for 6 years and 10 months
9	55	F	1.4×0.9×0.8	body	distal pancreatectomy	single adenoma	(+)	healthy for 6 years and 3 months
10	29	F	1.2×0.8×0.6	body	distal pancreatectomy	single adenoma	(–)	healthy for 5 years and 4 months
11	45	F	0.7×0.7	body	distal pancreatectomy	single adenoma	(–)	healthy for 4 years and 7 months
12	64	M	2×1.8×1.5	tail	distal pancreatectomy	single adenoma	(–)	healthy for 1 years and 9 months
13-I	44	F	1.3×1×0.8, 0.8×0.5×0.4	body, tail	distal pancreatectomy	multiple adenoma, MEN- I	(–)	recurrence of hypoglycemic attack at 3 months
13-II	53	F	2×1.5×2	head	PPPD	single adenoma	(+)	healthy for 6 months

Table 2. Results of true-positive rate of preoperative radiographic tumor localization studies.

Localization study	Positive studies (%)
PTPVS	6/7 (86%)
Angiography	8/15 (53%)
US	6/11 (55%)
EUS	4/4 (100%)
CT	3/10 (30%)
MRI	2/2 (100%)

PTPVS; percutaneous transhepatic portal venous sampling, US; ultrasonography, EUS; endoscopic ultrasonography, CT; computed tomography, MRI; magnetic resonance imaging.

tumor in the head of the pancreas, although other localization test procedures failed.

SURGERY

At surgery, the tumors were identified and resected in all patients. The tumors were evenly distributed through the pancreas and ranged from 0.1 to 3.5 cm, with most between 1 and 2 cm. The tumor was visualized by IUS in 6 of 6 patients (No.8, 9, 10, 11, 12, 13-II.100%). IUS found the tumor in 2 patients who did not have a palpable tumor (2 out of 6 patients). IUS was also particularly helpful in identifying nonpalpable tumors in the head of the pancreas. The tumors were removed by enucleation, if IUS determined the relationship of the tumor to the pancreatic duct, or by pancreatic resection, if it did not. Six patients underwent enucleation, 6 patients underwent distal pancreatectomy, 2 patients underwent subtotal (80%) distal pancreatectomy and one patient a pylorus preserving pancreaticoduodenectomy (PPPD) (Table 1). Patients No.10 and No.12 had pancreatic fistulas. These complications were resolved without long-term sequelae. Two patients (patients 6 and 13) underwent reoperations.

PATHOLOGY

Eleven patients had single adenomas. Two patients had multiple adenomas. One of these patients had parathyroid hyperplasia and pituitary adenoma, and belonged to the multiple endocrine neoplasia (MEN) I group.

FOLLOW-UP

Mean follow-up of the patients still living in 1997 was 9 years. One patient was found to have died

due to perforation of a duodenal ulcer, while another had died of hepatic failure caused by liver cirrhosis. In this patient, advanced liver cirrhosis was observed at the time of the operation for insulinoma. The development of iatrogenic diabetes mellitus occurred in the cases of 3 patients after the operation. We would like to show one reoperative insulinoma (Case 13). Case 6 was previously described in detail[9].

CASE REPORT

A female aged 44 years was referred to our university hospital due to a hypoglycemic attack. Twelve years before, a pituitary adenoma had been extirpated in the Hiroshima city hospital. PTPVS suggested that the tumor was probably located in the body and tail of the pancreas. In January, 1988, this patient had parathyroid hyperplasia and belonged to the MEN-I group. In August, 1988, distal pancreatectomy was performed. Macroscopically, two tumors were resected. However, microscopically multiple islet tumors were observed. Two weeks after the operation the FBS level dropped to 40 to 50 mg/dl. Three months after the operation, EUS showed a pancreatic head tumor. In January, 1997, endoscopic shock wave lithotomy (ESWL) treatment was performed for common bile duct stones and renal stones. The frequency of the hypoglycemic attacks was increasing and obesity was marked (120 kg). She was thus introduced for surgical treatment of recurrent insulinoma. In September, 1997, PPPD was undertaken. Two months after the operation, she was discharged. She was healthy, and DM was controlled by subcutaneous insulin injection therapy.

DISCUSSION

Insulinoma are rare with an estimated incidence of four per million population per year[12]. It is reported that among 95% patients with insulinoma, 84% were benign tumors, while 16% were malignant tumors, and 83% were single-onset and 13% were multiple, the remaining 4% being multiple endocrine adenomatosis[13]. In our series, 11 cases were single-onset tumors, one case (case 6) was multiple and one case was insulinoma associated with MEN type-I.

The success of the diagnostic imaging studies (US, CT, MRI, angiography and PTPVS) in this group of patients was almost compatible with that reported in previous studies[2,3,5,7,13]. The results of noninvasive localization techniques, US and CT have been discouraging, and sensitivities ranging from 0% to 62% (mostly about 30%) have been reported[3,8,16]. MRI has proved helpful for detecting insulinoma, although the number of MRI employed in this study was very small. MRI has not yet been widely evaluated for its utility. In other situations the true-positive rate ranged from 0% to 25%[5,16]. Further studies are necessary to determine the utility of MRI. Because of these poor results, the invasive radiologic technique is generally used. As a result of the vascularity of insulinomas, angiography has been successful in localizing the tumor "blush"[1]. Angiography correctly identified tumor in 53% of the patients. PTPVS has proved very helpful for detecting insulinomas. Other institutions have reported a successful localization rate of 64% to 100%[3,16]. Doherty et al[5] reported that PTPVS provided valuable information in a reliable fashion for a majority of patients with insulinomas, which are apparently difficult to image by other standard radiologic examinations. Thompson et al[14], however, have not been convinced that the time, effort, cost, and morbidity of such an invasive procedure are justified when they directly influence decision-making at the time of operation in only an occasional patient. These results may suggest that PTPVS continues to be the most sensitive preoperative study available for insulinoma localization, despite its disadvantages. Most recently, EUS has been advocated for the localization of insulinomas. Rosche et al[10] correctly localized 33 to 39 tumors with only one false-positive result in 19 normal patients. Pedunculated tumors and tumors in the tail are difficult to localize by this modality, but these should be more easily recognized by careful mobilization, palpation and the use of IUS. Since 1991, we have routinely used IUS for the operative exploration for insulinoma. In 6 of the 6 patients in this study, the localization of the tumor was identified by IUS. IUS found the tumor in 2 patients who did not have a palpable tumor in this study and was clearly more effective than palpation alone. IUS appeared particularly helpful in identifying tumors in the head of the pancreas and in defining the relationship of the tumor to the pancreatic duct[8]. At other institutions, IUS has been a useful adjunct to exploration, and the tumor was visualized by IUS in 75 to 100% of cases[3,5,8]. These results appear to corroborate our conclusion that IUS has an essential role in the operative exploration for insulinoma.

Excluding malignant insulinomas, very high cure rates (90% or more) have been reported[11,14]. Despite these successes, 10% to 20% of insulinomas remain occult to palpation. Operative failures occur principally because of surgically occult tumors, with a minority caused by multicentric disease (sporadic MEN 1) and malignancy[14]. In a large multicentric international review of 396 patients (1977 to 1987) who had undergone operation for benign insulinomas, 35(9%) patients underwent reoperation for persistent disease[11]. Two cases (15%) among our patients were reoperated for persistent disease after initial operations. Thompson et al[14] also reported that operation morbidity increased from 21% to 58% with reoperation

by analyzing 313 patients with insulinomas. In our reoperated cases, no complications were observed in the postoperative period. It has been suggested that when insulinomas are multiple in an adult patient, one should strongly consider the diagnosis of MEN-I[4]. Not all patients with multiple insulinomas, however, have MEN-I. A series of 72 patients with insulinomas reported by van Heerden et al[15] included eight patients with multiple insulinomas, of whom three had MEN-I. In all, 4% of insulinomas occur in patients with MEN-I[13]. From the viewpoint of surgical treatment for insulinoma associated with MEN-I, Demeure et al[4] advocated the need for a different surgical approach. Because insulinomas in MEN-I are likely to be multiple, enucleation and local resection would fail. They recommended subtotal pancreatectomy and enucleation of any tumors identified in the head of the pancreas in patients with insulinoma and MEN-I[4]. In case 13, we were able to discover two insulinomas, and distal pancreatectomy was performed at the initial operation. However, pathology revealed multiple islet tumors. Two weeks after the operation, the FBS dropped to 40 to 50 mg/dl. EUS and IUS showed a deep-rooted pancreas head tumor near the main pancreatic duct. As a result, PPPD was performed (total pancreatectomy). Although she has been free of symptoms for 6 months after the operation, careful observation has to be continued. These results may indicate the need for an aggressive surgical procedure in the case of multiple adenoma or insulinoma in MEN-I.

Diabetes is uncommon after the initial operation for insulinoma, but the incidence increases after reoperations. Thompson et al[14] reported that the development of iatrogenic diabetes mellitus occurred in 13 patients (33%) after reoperation of 39 patients. In our study, three patients developed diabetes mellitus, two patients after distal pancreatectomy, and one patient after reoperation of PPPD. However, all three patients are healthy and live a normal life.

This evaluated experience with a referral population of patients with insulinoma led us to conclude that (1) PTPVS and probably EUS may be the most sensitive preoperative study available for insulinoma localization, (2) IUS should play an essential part in the operative exploration for insulinoma, and (3) an aggressive surgical procedure is necessary in the case of multiple adenoma or insulinoma in MEN-I.

(Received March 5, 1998)
(Accepted May 19, 1998)

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