World J Surg
DOI 10.1007/s00268-007-9390-y

World Journal of Surgery

Management of Insulinomas: Analysis from a Tertiary Care Referral Center in India

Thomas V. Paul · Jubbin J. Jacob · Senthil K. Vasan · Nihal Thomas · Simon Rajarathnam · Ben Selvan · M. J. Paul · Deepak Abraham · Aravindan Nair · M. S. Seshadri

Abstract The aim of this study was to describe the localization and management of patients with pancreatic insulinomas and determine the most effective localization and surgical techniques in the presence of significant financial constraints in the patient population. We retrospectively reviewed the case records of 18 patients with insulinomas treated at our institution over a period of 10 years. The medical records were reviewed for demographic data, clinical presentation, biochemistry, details of localization studies, intraoperative findings, postoperative outcome, and long-term follow-up. The sensitivities of the various localization procedures were calculated using the intraoperative findings as the gold standard. There were 10 men and 8 women in the study, with a median age of 43 years. All patients underwent a supervised 72-hour fast and developed symptomatic hypoglycemia within 48 hours. An average of 1.9 localization procedures was performed per patient. Computed tomography (CT) had a sensitivity of 62% and specificity of 100%. Magnetic resonance imaging and digital subtraction angiography had specificities of 85% and 100%, respectively, with a specificity of 66% and 50%, respectively. Fourteen patients underwent surgery. Intraoperatively the excised tumor was palpable in nine patients, and all patients had postoperative euglycemia. In five patients the tumor was not palpable during the time of surgery; three of these patients underwent blind distal pancreactomy, with two patients having persistent hypoglycemia during the postoperative period. Two patients had a negative exploratory laparotomy. Patients with a surgical cure were followed up for a mean period of 24 months. On the background of financial constraints in connection with patient care, CT scanning is a cost-effective option with good specificity. Intraoperative palpation of the tumor and enucleation is the most effective technique for surgical cure. Blind distal pancreactomy is not advocated for tumors that are not localized intraoperatively.

T. V. Paul · J. J. Jacob · S. K. Vasan · N. Thomas (✉) · S. Rajarathnam · M. S. Seshadri
Department of Endocrinology, Christian Medical College and Hospital, Vellore 632004, India
e-mail: nihal_thomas@yahoo.com

T. V. Paul
e-mail: thomasvpaul@yahoo.com

B. Selvan · M. J. Paul · D. Abraham · A. Nair
Department of Surgical Endocrinology, Christian Medical College and Hospital, Vellore 632004, India

Insulinomas are uncommon endocrine tumors that have a prevalence of around 1 per 100,000 person-years [1]. However; they represent the most common functioning endocrine tumor of the pancreas (accounting for 42% of pancreatic endocrine tumors). They are typically single, small, and hypervascular, with 90% measuring <2 cm and 30% measuring <1 cm in diameter. Approximately 10% are multiple, 10% are malignant, and 16% are associated with multiple endocrine neoplasia type 1 (MEN-1) [2]. Even though these tumors are small, their functionality is responsible for their early presentation.

Our ability to manage this disorder has advanced over the years. Several options are available at present for preoperative localization of the tumor. However, the available options do not exceed the sensitivity of intraoperative

palpation and ultrasonography of the pancreas by a skilled surgeon [3].

In this article we attempt to characterize the disease, calculate the sensitivity of the various localization procedures, and assess the outcome of surgery.

Patients and Methods

From 1995 to 2005, a total of 18 patients were suspected to have an insulin-producing pancreatic tumor based on documentation of Whipple's triad. The medical records of these patients were reviewed for demographic data, clinical presentation, biochemistry, details of localization studies, intraoperative findings, postoperative outcome, and long-term follow-up. Altogether, 14 of them underwent surgery; the other 4 patients opted for medical treatment. All patients had some form of localizing procedure performed before surgery. The sensitivity, specificity, and positive predictive values were calculated using standard formulas. The data was analyzed using the Statistical Program for Social Sciences (SPSS Version 11.0 for Windows; SPSS, Chicago, IL, USA).

Results

Demographic Data

Ten men and eight women had insulinomas. The youngest patient was 20 years old and the oldest was 70. Details are given in Table 1. Both the mean and median age at the time of presentation were 43 years. Two patients had MEN-1.

Clinical Presentation

Most patients were referred to our center for management of symptomatic hypoglycemia. In total, 64% of these patients had a documented episode of hypoglycemia prior to presentation to our center. In the remaining patients, the initial detection of hypoglycemia was established at our center. The details of symptoms experienced by the patient are outlined in Table 2. Unusual presentations included a patient who was noted to have wasting of the small muscles of the hand related to hypoglycemic neuropathy (Fig. 1).

Although most patients (64%) had documented hypoglycemia prior to presentation to our center, all patients underwent a supervised 72-hour fast. They all developed symptomatic hypoglycemia within 48 hours of the fast. The lowest glucose levels noted during the fast ranged from 20 to 45 mg/dl. Concomitant serum insulin levels were available for 15 of the 18 patients. The mean ± SD insulin level was 56.9 ± 39.7.

Localization Procedures

Once a proven episode of hypoglycemia was documented, preoperative localization procedures were performed. The choices included a CT scan (Fig. 2) of the abdomen ($n = 13$), magnetic resonance imaging (MRI) scan of the abdomen ($n = 12$), and digital subtraction angiography (DSA) ($n = 7$). The expertise and the acquisition of endoscopic ultrasonography (US) were available only during the later phase of the study period. Endoscopic US (EUS) was performed in 3 patients and the tumor was localized in all of them. A total of 35 localization procedures were done on 18 patients, which worked out to an average of 1.9 tests per patient. The accuracy of the various tests are summarized in Table 3 based on histopathologic confirmation of the tumor among operated patients.

Surgical Findings and Outcomes

There were a total of 18 patients, 14 of whom had undergone surgery (7 enucleation, 2 distal pancreatectomy, 3 blind distal pancreatectomy, 2 explorative laparotomy). Surgical cure was defined as confirming the presence of the tumor on histopathologic examination and return of plasma glucose to the normal level without subsequent hypoglycemic episodes. Eleven subjects (71%) had a surgical cure: seven had undergone enucleation, two had distal pancreatectomy, and two had blind distal pancreatectomy. Of the three patients who underwent a blind distal pancreatectomy due to failed preoperative localization, two had a surgical cure. Among the three patients with failed surgeries, there was one (who underwent blind distal pancreatectomy) in the preoperatively nonlocalized group and two in the preoperatively localized group. The four patients who did not undergo surgery were kept on oral antihypoglycemic agents. In our experience, preoperative localization appears mandatory for a successful outcome, and it is more relevant in the laparoscopic era.

Pathologic Features

Of the 14 patients who were operated on, distinct islet cell tumors were identified in 11, one of which was malignant; no lesion was identified in the excised tissue from the other 3 patients. Among the benign tumors, five were located in the head, three in the tail, and one in the uncinate process. One malignant tumor was identified in the neck of the pancreas. In this specimen, there was nuclear pleomorphism and hyperchromatism in addition to the presence of tumor emboli in the vascular channels. There was no

Table 1 Summary of variables of patients with insulinoma

Pt. no.	Age (years)	Sex	72-Hr Fast		Localization				Surgery and Outcome					
			Insulin levels (μU/ml)	Lowest plasma glucose levels (mmol/L)	CT abdomen	DSA	MRI abdomen	Angiogram	Preop localization	Surgery	Intra operative findings	Post Operative status	Histology	Post operative Medical Therapy
1	30	M	NA	2.2	Normal	–	–	–	No	Tumour Excision	Tail	Normoglycemic	No Tumour	–
2	53	M	NA	2.4	Uncinate	–	–	–	Yes	Tumour Excision	Uncinate	Pancreatitis Normoglycemic	Benign	–
3	65	M	NA	1.1	Head & Tail	–	–	–	Yes	Enucleation	Head & Tail	Upper GI Bleed / LVF, Acute Renal Failure Normoglycemia Expired	Benign	–
4	36	F	50	1.9	Normal	Tail	Neck	–	Yes	Enucleation Distal Pancreatectomy	Neck	Pancreatits Septicemia Normoglycemia	Malignant	–
5	70	F	29	1.9	Normal	–	Normal	–	No	No Surgery	NA	NA	NA	Diazoxide
6	49	F	62	2.2	–	–	Head	–	Yes	Tumour Excision And Roux En Y Pancreatico Jejunostomy	Head	Normoglycemia	Benign	–
7	61	F	13	2.0	Head	Head	Head	–	Yes	Tumour Excision	Head	Normoglycemic	Benign	–
8	64	M	97	1.5	–	–	Body	–	Yes	Blind Distal Pancrectomy	Not Localised			
										Normoglycemic	No Tumour	–		
9	49	F	81	1.8	Tail	–	Tail	Tail	Yes	Tumour Excision	Tail	Normoglycemic	Benign	–
10	43	M	37.8	1.6	–	Tail	Tail	–	Yes	Distal Pancrectomy	Tail	Normoglycemic	Benign	–
11	20	F	55	2.0	Normal	–	Normal	Normal	No	Blind Distal Pancrectomy	Not Localised			
										Normoglycemic	No Tumour	–		
12	34	M	27	2.0	–	Head	Head	–	Yes	Exploratory Laparotomy	Not Localised			
										Hypoglycemia	No Tumour	Phenytoin Sodium		
13	28	M	29	1.8	–	–	Head	–	Yes	No Surgery	NA	NA	NA	Phenytoin Sodium
14	21	M	62	1.5	Normal	–	–	–	No	Enucleation	Head	Normoglycemic	Benign	–
15	29	F	84	2.0	Normal	–	Normal	Normal	No	Blind Distal Pancrectomy	Not Localised			
										Hypoglycemia	No Tumour	Diazoxide -		
16	45	M	10.9	1.8	Uncinate	–	–	–	Yes	No Surgery	NA	NA	NA	Diazoxide
17	35	F	50.3	2.0	Normal	–	–	–	No	No Surgery	NA	NA	NA	Diazoxide
18	44	M	167	2.2	Uncinate	–	Normal	–	Yes	Enucleation	Uncinate	Normoglycemia Sec Hemmorhage	Benign	–

NA, not applicable; CT, computed tomography; DSA, digital subtraction angiography; MRI, magnetic resonance imaging; PCT, pancreactomy; LV, left ventricular; LVF, LV failure

Table 2 Details of symptoms experienced by the patients with insulinoma

Symptoms	No of patients
Neuroglycopenic symptoms	18 (100%)
Weakness or dizziness	14 (77.7%)
Seizures	6 (33.3%)
Loss of consciousness	13 (72.2%)
Autonomic symptoms	17 (94%)
Palpitations	14 (77.7%)
Diaphoresis	15 (83.3%)
Weight gain	5 (27.7%)

Fig. 1 Photograph of the hand of a patient with hypoglycemic neuropathy reveals wasting of the small muscles of the hand

regional lymphadenopathy. The mean size of the tumors was 2.4 cm (range 1.5–5.0 cm).

Intraoperative Management

Dextrose (10%) was started in all patients on the night prior to the surgery and was withdrawn during surgery. Glucometer sugars were monitored periodically. A bilateral rooftop incision was made in all the patients. The pancreas was skeletonized and bimanual palpation performed. In two patients an additional nodular thickened area in the pancreas was felt in addition to the tumor. Intraoperative ultrasonography (IOUS) was used in 11 of the 14 patients (78%). Although there was US localization in one patient, the histopathologic examination was negative for tumor. The combined bimanual palpation with IOUS had a sensitivity of 98%. According to the published literature, the role of frozen section in the perioperative diagnosis of insulinoma is limited. However, in our experience, particularly in doubtful situations, a frozen section was found to be helpful. All patients underwent a frozen section examination.

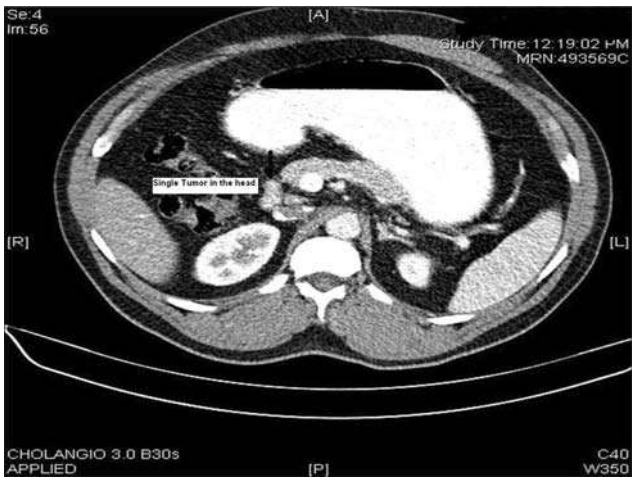

Fig. 2 Computed tomography scan showing a single tumor in the head of the pancreas

Postoperative Complications

There was a single postoperative death (8%). The subject had underlying cirrhosis of the liver. Other complications included pancreatitis, hemorrhage, pancreatic fistula, and lung complications including pneumonia and atelectasis. Two patients developed postoperative pancreatitis; one of the patients settled through conservative management and another required cystogastrostomy as a second-stage procedure. One patient developed secondary hemorrhage on the first postoperative day that required reexploration. Four patients (29%) developed a pancreatic fistula, and one had a pancreatic pseudocyst. One of them had a major duct leak that warranted reexploration and pancreaticojejunostomy; she had an uneventful postoperative period. This patient had malignant insulinoma on histopathology. Lung complications secondary to postoperative atelectasis and pneumonia were seen in 29% of the patients.

Other Coincident Endocrine Tumors

Two patients in the series had MEN-1 syndrome. The first patient was a 43-year-old man who underwent parathyroid surgery for parathyroid hyperplasia 3 years prior to presentation with symptomatic hypoglycemia. The second patient was a 35-year-old woman in whom a microprolactinoma was detected during a workup for symptomatic hypoglycemia. Genetic studies were not done.

Follow-up

The period of follow-up ranged from 2 months to 12 years (mean 27 months). Two patients were lost to follow-up

Table 3 Details of localization procedures undertaken in patients with insulinoma

Modality	No. of operated patients	Results				Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Cost of procedure
		TP	FN	FP	TN				
Helical CT scan	10	5	3	0	2	62.5	100	100	Rs 8000 (US $178)
MRI scan	10	5	1	2	2	83.3	50	71.4	Rs 8750 (US $195)
DSA	7	3	0	2	2	100	50	60	Rs 24,000 (US $535)

TP: true positive; FN: false negative; FP: false positive; TN: true negative

after the immediate postoperative period. Among the patients who did not undergo surgery, one patient is not on long-term follow-up, whereas the other three are followed up regularly. Two of these patients are on phenytoin therapy and one on diazoxide therapy over the past 6 years. Patients who had successful surgical outcomes had a median follow-up of around 12 months. Of the patients not cured by surgery, two are on medical therapy with a mean follow-up of 32 months.

Discussion

Although insulinomas are the most common clinically functioning islet cell tumor of the pancreas, the lesion is still uncommon [4], comprising 42% of the total endocrine tumors of the pancreas. Preoperative localization is the most important factor in regard to surgical outcome [5].

Abdominal US provides disappointing results, with only 30% sensitivity [6]. The MRI scan has not shown promising results, with the exception of mangafodipir-enhanced MRI, fast spin-echo, fat saturation, and dynamic contrast-enhanced scans [4–10]. Otherwise, the acceptable sensitivity pattern for MRI scan ranges from 35% to 45% [10, 11]. Endoscopic US (EUS) may pick up suspected lesions in head and body and has a sensitivity of 80% to 90% [12, 13]. However, if the lesion is in the tail of the pancreas, the sensitivity drops to 37% to 60%. The tumor is likely to be difficult to interpret if it is pedunculated, isoechoic, or in the distal pancreas; moreover, it is observer-dependent [1, 13]. The modified Doppman and Imamura SASI test (selective arterial secretin injection test) or ASVS (intra-arterial calcium stimulation with hepatic venous sampling) should be reserved for patients with nesidioblastosis, failed preoperative localization with other modalities, or failed surgery and in those with MEN-2B, which is known to have multiple tumors [14–18]. With any of the given modalities, failure to localize preoperatively lies between 20% to 30% [19–22]. In our series, five patients (28%) had failed preoperative localization.

The analysis of our experience with the management of insulinoma revealed baseline patient characteristics that are similar to those in other large series from developing and developed countries. The mean age of presentation of 43 years in our series is similar to the mean age of 41 to 47 years reported form other series [23–25]. A male preponderance was noted in our series, contrasting with many Western series with female preponderance (1.0:1.4) but similar to series from other Eastern countries [13, 26–28]. All patients had a positive Whipple's triad on a supervised 72-hour fast [9]. Symptomatic hypoglycemia was achieved within 48 hours of initiation of the fast in all 18 of our patients with insulinoma.

The standard protocol followed after establishing the fact of hyperinsulinism in the presence of symptomatic hypoglycemia is to order a localization procedure. The procedure usually ordered first is either CT or MRI of the pancreas. If the tumor is not localized by either of these tests, DSA is performed. In some of these patients, particularly over the last few years, we have performed EUS. The calculated sensitivities of CT, MRI, and DSA in this series were 62.5%, 85.7%, and 100%, respectively. The improvement in sensitivity with the more advanced localization techniques was at the cost of declining specificity. The specificities of CT, MRI, and DSA were 100%, 66%, and 50%, respectively. Of the three localization procedures done, CT had the highest positive predictive value (PPV) (100%). Pathologically, 10% (1/10) of the identified tumors were malignant, and 14% (2/14) of the operated patients had multiple tumors.

Localization of Insulinomas Under Resource Constraints

Computed Tomography is safe, simple to perform, operator-independent, and widely available in most developed and developing countries. For these reasons, CT scanning is the most widely used initial noninvasive technique for localizing insulin-producing islet cell tumors. The CT image, in addition to locating the tumor, visualizes the relation of the tumor to vital structures and the presence of extrapancreatic metastasis. A wide range of sensitivities have been reported with the use of CT scanning for

localization of insulinomas, from a dismal 16% to 72% [11, 13, 25–29]. This variability of sensitivity over the years has been attributable to the advent of more advanced multislice CT scanners. Selective arterial calcium infusion and DSA were done during the early phase of our series. However, with the advent of a newer generation of CT scans, these tests should be reserved for patients who had a failed surgical exploration or multiple endocrine tumors and when other modalities fail to localize tumors preoperatively [14, 15]. Recent reports from China and Brazil have highlighted improved sensitivity with helical CT scanning and use of bolus timing to 63.4% and 71.42%, respectively [30, 31].

Over the last two decades we have utilized both conventional CT and helical scanning to arrive at a sensitivity of 62.5%. However, it is of greater importance that the accuracy of the technique (PPV 100%) enhances the value of a positive localization to the operating surgeon. This accuracy was demonstrated in the Brazilian series as well [32].

The sensitivity of arteriography, which was once considered the "gold standard," has shown wide variations, from 29% to 64%, since the initial publications on its use [12, 14, 15]. However Geoghegan et al. had accurately identified all insulinomas in their series using magnification, subtraction films, superselective arterial catheterization, and oblique views [16]. This highlights a basic problem with arteriography; it has wide variation in sensitivity depending on the skill of the operator and the experience of the center undertaking the procedure. In our center, the sensitivity of DSA was 85.7% but a specificity of 50% and a PPV of 50%. Therefore, it may not be cost-effective in a setup where there are financial limitations for the patients.

Laparoscopic techniques have been evolving over time. An analysis from the literature regarding laparoscopic techniques clearly shows that major resections are done more commonly than enucleation when compared to open operations [26–28]. This may be because of the technical difficulties that are faced during enucleation of the embedded lesions. To achieve better accuracy in localization, one should have available laparoscopic US with the personnel who have adequate skills to operate it. There is a marginal reduction in the fistula rates among the patients who were undergoing laparoscopic excision (18%). The overall acceptable minor fistula rate is around 20% 30% [29–31, 33].

Over the past decade most centers dealing with insulinomas have abandoned the practice of blind distal resection and have opted for more invasive and sensitive localization techniques [21, 22]. For most of the previous decade, however, blind distal resection has been considered the standard of care in the management of the patients with occult insulinomas [23, 24]. This procedure was done in three of our patients, resulting in a 67% cure rate and recurrence of symptoms in the remaining 33%. If the tumor is not localized intraoperatively, blind resection should not be performed; the patient should be put on medical management for the hypoglycemia and the ASVS test done [1].

Conclusions

A supervised 72-hour fast, performed as an inpatient procedure, with a demonstration of Whipple's triad is feasible in most centers. Localization should be attempted with helical CT of the pancreas, with thin slices taken during the arterial phase of contrast infusion. Intraoperative palpation of the pancreas along with IOUS may improve the sensitivity up to 98%. At present, laparoscopic surgery is considered to be the gold standard. There is no role for blind resection in a patient with failed intraoperative localization. Further improvements in surgical cure rates may be possible with better preoperative localization methods. Hepatic venous sampling after calcium stimulation, though sensitive, may not be cost-effective under resource constraints and should be reserved for those who have failed surgery.

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