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REVIEW OF EIGHT CASES OF INSULINOMA
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REVIEW OF EIGHT CASES OF INSULINOMA

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ABSTRACT

Objective: **To review patients records operated with the diagnosis of insulinoma and to discuss their clinical presentations, diagnostic and therapeutic modalities.**
Design: **Retrospective study.**
Setting: **Ankara Numune Teaching and Research Hospital, Turkey.**
Subjects: **Eight cases were operated in the Department of 6th Surgery, Ankara Numune Teaching and Research Hospital between 1994 and 2000. All patients had neuroglycopenic symptoms. Six patients had blood glucose levels of lower than 50 mg/dL during the admission. The other two patients had hypoglycaemia in the prolonged fasting test. Serum insulin/glucose ratio was diagnostic in all patients except one. Abdominal ultrasonography and computerised tomography could successfully localise the tumour in one case. In six patients tumours could be localised by endoscopic pancreatic ultrasonography. In one patient none of the studies could localise the tumour. Three tumours were located at the pancreatic head, one in the neck, two at the body and two at the tail. All tumours except one were palpable. Enucleation was the procedure of choice in four cases and distal pancreatectomy was the procedure of choice in four.**
Results: **Post-operative course was uneventful in seven patients. One patient died due to intra-abdominal sepsis. Hypoglycaemia was controlled in all patients after the surgery.**
Conclusion: **Surgery is the mainstay of treatment of insulinoma. Enucleation should be the procedure of choice if possible. Endoscopic pancreatic ultrasonography has promising results and may replace invasive angiographic studies in the future.**

INTRODUCTION

Insulinoma is derived from pancreatic ß-cells and it is the most common pancreatic islet cell tumour. Its incidence is approximately four per 5 million of population(1). Although it can be seen at any age(2) the mean age at presentation is 45 years with female preponderance(1). The majority of insulinomas are benign and solitary(2) but they may be multiple, diffuse, small sized or even nesidioblastosis(3,4). Diagnosis is often delayed and the clinical presentation is not correlated with the size or the malignant potential of this tumour. Symptoms are generally due to hypoglycaemia. The diagnosis of an insulinoma is usually a chemical one(2). The tumour is almost always located in the pancreas(5) and extra-pancreatic involvement is rare(4). Pancreatic head, body and tail are equally involved and many invasive or non-invasive investigations can be done to localise or regionalise the tumour in the pancreas prior to surgery(1). Although the majority of insulinomas are benign and solitary(2) 5-15% are reported to be malignant(4). Medical therapy can control hypoglycaemia in 60% of cases but the mainstay of treatment is still surgical excision(1,6,7). The tumour can be located anywhere in the pancreas and many invasive or non-invasive pre-operative and intra-operative localisation studies have been so far used. In this retrospective analysis of eight cases, clinical presentation, preoperative localisation and surgical alternatives are discussed in dealing with insulinoma.

MATERIALS AND METHODS

Six male and two female patients were operated with the diagnosis of insulinoma in the 6th Department of Surgery, Ankara Numune Teaching and Research Hospital between 1994 and 2000. Mean age of presentation was 39 (22 to 59) years. Mean interval between the onset of symptoms and clinical admission was 48 (1.5 to 120) months. Seven patients were admitted to evaluate the cause of hypoglycaemia and one was admitted with coma to the neurology department. All patients had neuroglycopenic symptoms. Loss of consciousness, hunger, dizziness, sweating, palpitation, weakness and coma were the symptoms and signs related with the disease (Table 1).

Table 1

Signs and symptoms of insulinoma

Symptoms and Signs	No. of Patients (n=8)	%
Loss of consciousness	7	87.5
Hunger	6	75
Dizziness / weakness	4	50
Sweating, palpitation, vertigo	3	37.5
Anxiety, confusion, personality changes	1	12.5
Coma	1	12.5

All patients except one were primary cases and first evaluated in our institution. In one case, pancreatic body and tail resection had been performed in another institution three years before presentation. The patient was referred to our hospital for ongoing symptoms and signs of hypoglycaemia after the primary operation.

Various laboratory studies had been performed to evaluate the patients. Fasting blood glucose levels, serum C-peptide and insulin levels were determined. Prolonged fasting test was performed in two patients who had blood glucose levels more than 50 mg/dL in the admission.

After biochemical evaluation, various techniques were used to localise the tumours. Abdominal ultrasonography (US), computed tomography (CT), endoscopic pancreatic ultrasonography (EUS) were the tests performed. Magnetic resonance imaging and invasive angiographic studies including selective celiac and superior mesenteric arteriography, percutaneous transhepatic portal venous sampling, arterial stimulation and venous sampling were not used as diagnostic tests for localisation of the tumours.

After the biochemical evaluation and localisation studies, patients underwent surgery for tumour removal. Intra-operative ultrasonography (IOUS) was not used during the surgical procedures. A good exposure of pancreas was obtained after opening the gastrocolic ligament and performing a wide Kocher manoeuvre. If the tumour could not be localised at this step, pancreatic body and tail mobilisation was performed to provide bi-manual palpation. Type of the surgical procedure was tailored up to the localisation and operative findings in each case.

RESULTS

Biochemistry: Six patients had blood glucose levels of lower than 50 mg/dL during the admission. The other two patients had hypoglycaemia in the prolonged fasting test. Serum insulin/glucose ratio was diagnostic for insulinoma (>0.4) in seven cases (Table 2). Serum C-peptide levels were investigated in conjunction with glucose and insulin levels and were found to be within normal ranges in four out of eight patients. Serum insulin levels were equal or higher than 10 µIU/mL in all patients. Serum C-peptide levels were elevated in four patients and within normal ranges in the remaining four.

Pre-operative localisation: All patients underwent an US and CT as the initial imaging procedure. Both CT and US could successfully localise a tumour in only one case. This was a 3x4 cm tumour located at the head of the pancreas (Figure 1). In the other patients US and CT examinations revealed normal radiological findings.

When a tumour could not be visualised by US and CT, EUS was performed. This technique was able to establish the correct diagnosis in six cases out of the seven it was performed (Table 3; Figure 2). In one patient, a tumour could not be localised despite the biochemical diagnosis. This patient underwent exploratory laparotomy and a tumour was found in the neck of the pancreas.

Table 2

Insulin/glucose ratios and C-peptide levels

Patient	Insulin (µIU/m L)/ glucose (mg/dL)	C-Peptide (pmol/ml)
I.B.	47/35=1.34	4.0
R.Y.	30/38=0.78	2.3
A.Ö.	121/35=3.45	3.72
M.Ç.	10/9= 1.1	0.6
M.Ç.	10/46=0.21	0.55
	11/49=0.22	0.56
A.D.	14/30=0.46	1.0
L.K.	21/25=0.84	0.70
S.G.	75/39=1.92	4.0

Table 3

Localisation of pancreatic insulinomas with different techniques

Patient	Abdominal Ultrasono-graphy	Compute-rised Tomography	Endoscopic Pancreatic Ultrasono-graphy	Palpation
I.B.	-	-	+	+
R.Y.	-	-	+	+
A.Ö	-	-	+	+
M.Ç.	-	-	+	+
M.Ç.	-	-	+	+
A.D.	-	-	+	+
L.K.	+	+	NP*	+
S.G.	-	-	-	+

*NP = Not performed.

Figure 1

Computerised tomography appearance of an insulinoma located at the head of the pancreas

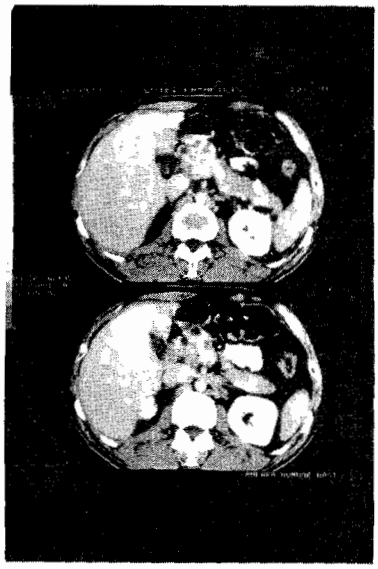
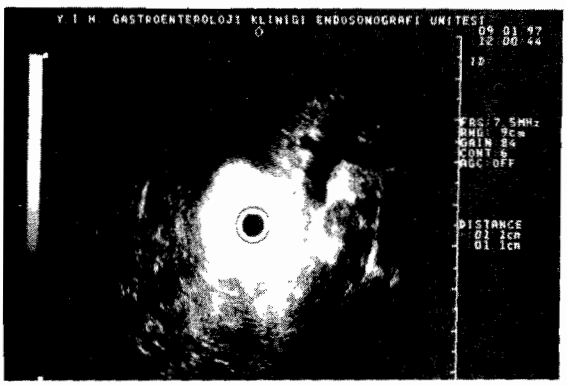


Figure 2

Endoscopic pancreatic ultrasonography of an insulinoma. Note the hypo-echogenic of the tumour



Operative intervention: In seven patients a tumour was localised prior to surgery. IOUS was not used during the surgical intervention. All tumours were confined to pancreas. Three tumours were located at the pancreatic head, one at the neck, two at the body and two at the tail. All tumours except one were palpable. Enucleation was the procedure of choice in four patients. Three of the enucleated tumours were located at the head and one at the neck of pancreas. Distal pancreatectomy was performed in four cases with tumours located at the pancreatic body or tail (Table 4). Splenectomy was added in two cases. This was due to iatrogenic splenic vein laceration in one. Distal pancreatectomy was performed in one case that the tumour was non-palpable. This tumour was previously localised at the tail of pancreas with EUS. A foreign body was discovered in the posterior omental bursa of the previously operated patient. This was surrounded with necrotic material and the foreign body was removed, then the cavity was debrided and irrigated. The tumour was at the pancreatic head which was enucleated.

Table 4

Tumour localisation, diameter and selected surgical procedure

Patient	Pancreatic Localisation	Diameter (mm)	Surgical Procedure
Î.B.	Head	12x9	Enucleation
R.Y.	Head	14	Enucleation
A.Ö.	Tail	11	Distal pancreatectomy+ splenectomy
M.Ç.	Tail	10	Distal pancreatomy
M.Ç.	Body	10	Distal pancreatectomy+ splenectomy
A.D.	Body	10	Distal pancreatectomy
L.K.	Head	30x40	Enucleation
S.G.	Body	20	Enucleation

Post-operative course: Post-operative course was uneventful in seven patients. Mean post-operative stay was 9.8 days (6-19). Hypoglycaemia was controlled in all patients after the surgery. One patient had high glucose levels requiring oral anti diabetic therapy. Pancreatic fistula formation was not developed in any case. Fever, leucocytosis, nausea and vomiting developed in the previously operated case. This patient was re-operated for upper gastrointestinal bleeding at the 17th day of surgery. A pancreatic abscess and peritonitis was discovered and drained. Truncal vagotomy and pyloroplasty was performed. The patient remained haemodynamically unstable after the operation and died at the postoperative day one.

Pancreatic islet cell tumours were detected in all specimens in the pathological examination.

DISCUSSION

Insulinoma, the most common pancreatic endocrine tumour is seen predominantly in females(2). In this series, however, all patients except two were male. Mean age of presentation was 39 years and this

was slightly younger than those reported in the literature(2). In general, majority of patients with insulinoma undergo extensive evaluation with the suspicion of a psychiatric disorder(6) and this is the cause of delay in the diagnosis. In this series, median interval between the onset of symptoms and the diagnosis was three years.

Two patients had glucose levels greater than 50 mg/dL at the admission. These patients had glucose levels lower than 30mg/dL in prolonged fasting. In a normal individual, insulin/glucose ratio should be less than 0.4; however in patients with insulinomas this ratio approaches to 1.0 and in some cases it may even exceed this level(8). This ratio was diagnostic for an insulinoma in all patients except one. In one patient however, insulin/glucose ratio was 0.21 and 0.22 despite re-evaluation. In most patients with insulinoma, plasma insulin level is usually greater than 10 µIU/mL(6). In this series mean insulin level was 37.6 (10-121) µ1U/mL.

Clandestical exogenous insulin administration may mimic the symptoms and signs of an insulinoma. This is called 'factious hypoglycaemia' and elevated serum levels of pro-insulin or C-peptide may exclude this diagnosis in insulinoma(4,6). Four of eight patients in this series however, had serum C-Peptide levels within normal ranges. It has been stated that approximately 13-22% of patients with insulinoma do not have elevated serum pro-insulin or C-peptide levels although in our series this ratio is 50%.

Once biochemically diagnosed, an insulinoma should be localised to enable appropriate surgical treatment. Wide spectrum diagnostic tests either invasive or non-invasive have been used for the localisation of insulinoma. An initial attempt should be made with US, as this technique is non-invasive, relatively cheap and easy to access. However it is operator dependent and this limits the value of this test(9). US should be followed by EUS, CT, MRI and arteriography(9). US has an average sensitivity of 50% (ranging 20-70%) (10) although the ability to image pancreas is limited by obesity and overlying bowel gas(6). The sensitivity of US decreases to less than 40% in tumours smaller than 1 cm. The localisation of insulinomas can be troublesome in the pancreatic tail(10). In our series only one patient with a tumour four cm in diameter located at the head of pancreas could be visualised by US. The same tumour was also identified by CT. CT and US are also useful for the identification of liver metastases(4). Magnetic resonance imaging has comparable sensitivity rates to that of CT(8,10).

EUS is safe and has increased sensitivity when performed by experienced users(2,6). It is highly accurate in the localisation of small pancreatic tumours and its use may reduce costs, save time and decrease patient morbidity generated by other more invasive diagnostic modalities(11). Tumours as small as 2-5 mm in diameter can be identified and the sensitivity range is 70-90%(6,7). EUS was diagnostic in six patients out of seven performed. In a recent study it has been stated that EUS-guided fine-needle aspiration can be performed to obtain tissue samples for the differentiation of benign and malignant disease(7).

In this series we managed to localise a tumour with US, CT or EUS in seven cases. The tumour that was not localised preoperatively was palpated during surgery. We did not perform any invasive angiographic tests as a localisation study. In the literature it has been stated that patients having tumours smaller than 2 cm that are not detected by non-invasive imaging tests should undergo invasive tests(6). An invasive angiographic intervention with or without stimulation with calcium has higher sensitivity rates of localisation when compared with the non-invasive techniques(6,8,12).

Arteriography alone detects fewer than 30% of the tumours smaller than 2 cm but combination with intra-arterial calcium injection increases the sensitivity up to 66%(12). This is called arterial stimulation and venous sampling (ASVS). Hyper-insulinism in multiple endocrine neoplasia type-1 (MEN-1) syndrome associated insulinoma may result from microadenomas, ß-cell hyperplasia and nesidioblastosis as well as a solitary adenoma(3). Transhepatic selective venous sampling (THVS) and IOUS may be of value in the localisation of such tumours (3). THVS is one of the most sensitive methods for regionalising an insulinoma(8) but it is an invasive, expensive and traumatic examination and should be performed only after a first surgical failure or when results of all other localisation procedures are negative (9).

Another way to locate otherwise occult insulinomas is IOUS(9). These tumours are often less than 1 cm in diameter. In addition IOUS can facilitate the identification of vital structures such as common bile duct, pancreatic duct or superior mesenteric vein during the operation(13). This is very important in selecting the appropriate surgical procedure for an insulinoma. The combination of IOUS and careful manual palpation by the surgeon can localise more than 95% of insulinomas(4). IOUS was not used in this series because this facility is not available in our institution.

Somatostatin receptors are found in tumours that arise in tissues also containing these receptors in normal life. Insulinomas contain these receptors but not octreotide receptors. Use of isotope-labelled somatostatin analogs for the visualisation of an insulinoma should be considered(14).

Medical therapy can control hypoglycaemia in 60% of cases but surgery is the definitive treatment(1,6,7). Cornstarch, diazoxide, calcium channel blockers, phenitoin and octreotide can be used successfully in some patients to control hypoglycaemia in some patients but short term medical therapy is especially useful to bridge a patient to surgical therapy. Long-term medical treatment has generally been

ineffective(6,12) and should be reserved for the few patients with unresected, unlocalised tumours despite thorough preoperative testing and exploratory laparotomy and for patients with metastatic, unresectable malignant insulinoma(6).

A bilateral subcostal or a median laparotomy should be done and an extended Kocher manoeuvre be performed. Posterior omental bursa is opened, spleen is mobilised and pancreatic tail and body is freed from the retroperitoneum for inspection and palpation. Once an insulinoma is located, enucleation or resection is considered up to the localisation of the tumour. An initial attempt should be made to enucleate the tumour(4,8). Most tumours can be enucleated, as they are compact in nature simulating encapsulation(4). But in patients with tumours located deep within the pancreas, tumours in conjunction with pancreatic or biliary ducts or in dealing with multiple tumours or hyperplasia of the pancreatic islets a resective procedure should be considered rather than enucleation(2). The association of multiple endocrine neoplasia type 1 (MEN-1) to insulinoma is very important because insulinomas may be multiple or diffuse(3,6). If the tumours are located within the body or tail of the pancreas a distal pancreatectomy is indicated(6). An occult insulinoma may be present despite all the diagnostic modalities performed. Blind distal pancreatectomy, intraoperative glucose monitoring or progressive pancreatectomy has been recommended for such tumours. Nowadays, blind distal pancreatectomy is not recommended for such cases. Instead, the operation should be terminated and ASVS should be performed for the regionalisation. At the re-operation this region of pancreas should be removed and this procedure is called 'enlightened resection' instead of 'blind resection'(1). In patients with multicentric insulinomas associated with MEN-I, there is no satisfactory surgical treatment if medical therapy fails. Total pancreatectomy and pancreatic transplantation may be of value in future in such cases(3).

REFERENCES

1. Dolan L. P. and Norton L. A. Occult insulinoma. *Brit. J. Surg.* 2000; **87**:385-387.
2. Menegaux E., Schmitt G., Mercadier M. and Chigot J. P Pancreatic insulinomas. *Amer. J. Surg.* 1993; **165**: 243-248.
3. Mignon M., Ruszniewski P., Podevin P., Sabbagh L., Cadiot G., Rigaud D. and Bonfils S. Current approach to the management of gastrinoma and insulinoma in adults with multiple endocrine neoplasia type I. *World J. Surg.* 1993; **17**: 489-497.
4. Grant C. S. Surgical management of malignant islet cell tumors. *World J. Surg.* 1993; **17**: 498-503.
5. Grant C. S. Surgical aspects of hyperinsulinemic hypoglycemia. *Endocrinology and Metabolism Clinics of North America.* 1999; **28**: 533-554.
6. Peplinski G., R., and Norton J. A. Endocrine tumours of the pancreas. In Breast and Endocrine Surgery, edited by John R. Farndon, pp. 143-176 London: W. B. Saunders Company, 1997.
7. Ardengh J. C., Rosenbaum P., Ganc A. J., Goldenberg A., Lobo E. J., Malheiros C. A., Rahal F. and Ferrari A. P., Role of EUS in the preoperative localization of insulinomas compared with spiral CT. *Gastrointestinal Endoscopy.* 2000; **51**: 552-555.
8. Wayne J. D., Tanaka R. and Kaplan E. L. In Textbook of Endocrine Surgery, edited by O.H. Clark, Q-Y Duh, pp. 577-591 Philadelphia: W. B. Saunders Company, 1997.
9. Pedrazzoli S., Pasquali C. and D'Andrea A. Surgical treatment of insulinoma. *Brit. J. Surg.* 1994; **81**:672-676.
10. Böttger T. C. and Junginger T. Is preoperative radiographic localization of islet cell tumors in patients with insulinoma necessary? *World J. Surg.* 1993; **17:** 427-432.
11. Bansal R., Tierney W., Carpenter S., Tompson N. and Scheiman J. M. Cost effectiveness of EUS for preoperative localization of pancreatic endocrine tumors. *Gastrointestinal Endoscopy.* 1999; **49**: 19-25.
12. Doppman J. L., Miller D. L., Chang R., Gorden P., Eastman R. C. and Norton J. A. Intraarterial calcium stimulation test for detection of insulinomas. *World J. Surg.* 1993; **17:** 439-443.
13. Zeiger M., Shawker T. H. and Norton J. A. Use of intraoperative ultrasonography to localize islet cell tumors. *World J. Surg.* 1993; **17**: 448-454.
14. van Eyck C. H. J., Bruining H. A., Reubi J.-C., Bakker W. H., Oei H. Y., Krenning E. P., Lamberts S. W J. Use of isotope-labelled somatostatin analogs for visualization of islet cell tumours. *World J. Surg.* 1993; **17**: 444-447.