**Background:** Insulinomas are rare tumors that are usually benign, single and curable by simple surgical excision. They can present problems in diagnosis and localization. **Study design:** Retrospective analysis of patients with insulinoma managed during a 13-year period (1992-2005) at a tertiary-level institution. **Results:** 31 patients (mean age 38.4 [SD 13.3] years; 16 men) presented with hypoglycemic symptoms for 4.6 (5.5) years. In 22 (71%) patients, the lesion was successfully localized pre-operatively. Of various preoperative localization techniques, CT angiography (5/6; 83%), intra-arterial digital subtraction angiography (11/17; 65%), dual-phase CT (8/14; 57%), and conventional MRI (4/13; 31%) had high rates of successful tumor localization. Intra-operative palpation and ultrasonography also had localization success rates (22/30 [76%], and 11/12 [92%], respectively); each identified one lesion that the other procedure did not localize. Of the 30 patients who underwent surgery, 28 had solitary tumor. **Conclusion:** Pre-operative investigations to localize insulinoma are helpful despite the availability of intra-operative ultrasound. Dual-phase CT should be the non-invasive investigation of first choice. [Indian J Gastroenterol 2006;25:244-247]

Insulinomas are rare tumors that occur in about 1 in 250,000 persons. They are often very small at presentation because of the potent effects of insulin secreted. Though functional and almost exclusively localized to the pancreas, they are often difficult to diagnose and to localize. Symptomatic hypoglycemic episodes are often non-specific, go unrecognized and are occasionally mistaken for seizures or psychiatric disorders for several years. There have been reports of long-standing insulinoma with marked adaptation to extreme hypoglycemia with near-normal plasma insulin levels.

Nearly 80% of these tumors are less than 2 cm in size and may not be easily seen on pre-operative imaging using CT, ultrasonography (US) or MRI. In addition, their identification at the time of surgery, except with the aid of intra-operative ultrasonography (IOUS), may be difficult because of their intra-parenchymal location and small size. About 10% of all insulinomas are malignant (with metastases) and 10% are multiple, with 50% of the latter being associated with the multiple endocrine neoplasia syndrome-1 (MEN-1).

There are few reports of insulinoma from India. We present a retrospective analysis of patients with insulinoma evaluated at a tertiary-care center.

**Methods**

Medical records of patients with insulinoma seen in the period 1992-2005 were retrieved from the hospital’s medical records department and the records of the Departments of Endocrinology, Gastro-intestinal Surgery and Radiology. From these, data on clinical and diagnostic features, localization and surgical outcome were extracted.

Pre-operative localization of tumor was attempted using a combination of radiological techniques available at the time of diagnosis, including trans-abdominal US, conventional contrast-enhanced CT scan (CECT till 2000), dual-phase CECT (since 1996), magnetic resonance imaging (MRI), conventional pancreatic arteriography (prior to 1994) and selective pancreatic arteriography (since 1994), namely, intra-arterial digital subtraction angiography (IADSA) with or without CECT (CT angiography till 2000). Subjects underwent surgery wherein lesions were identified based on a combination of pre-operative localization, intra-operative palpation of the pancreas and IOUS (since 2000).

**Results**

**Clinical characteristics**

Thirty-four patients with insulinoma (16 men) had been diagnosed over the 13-year study period. Details of three patients, including one with malignant insulinoma and another associated with parathyroid adenoma, were not available. All patients had presented with fasting hypoglycemia and fulfilled Whipple’s triad to suspect a diagnosis of insulinoma. The diagnosis had been confirmed by demonstration of inappropriately elevated plasma insulin levels during an episode of spontaneous hypoglycemia or pro-
The patients were aged 15 to 60 years (mean 38.4 [SD 14.3]). Average duration of symptoms was 4.6 (5.5) years (range 0.1-20). Frequency of hypoglycemic episodes at presentation ranged from daily (25 [83%] patients) to once a month. Eight (25%) subjects had permanent and severe cognitive dysfunction related to uncorrected hypoglycemia. Six subjects had received anti-epileptic drugs, 4 had received psychotropic drugs, and 2 had received both these sequentially.

**Biochemical diagnosis**

Twelve (39%) patients had spontaneous hypoglycemia during hospitalization and 19 (63%) required a prolonged fast to induce hypoglycemia. The mean duration of fast required in the latter group to induce symptoms was 20.4 (9.8) hours. The mean (SD) blood glucose level at the time of hypoglycemia was 25 (8) mg/dL (range 12-38) and concomitant mean plasma insulin was 44.9 (34.1) µU/mL (range 9.2-138.9). The mean insulin:glucose ratio was 0.8 (0.4) (range 0.25-1.52). Concomitant C-peptide levels was estimated in 3 subjects (0, 3.0, and 11.1 ng/mL; normal 1.1 to 4.4). Glycosylated hemoglobin levels was measured in five patients and ranged from 3.9% to 4.4% (normal 3.8%-7.3%).

**Pre-operative localization**

Dual-phase CT and IADSA had the highest sensitivity rate among all the pre-operative localization techniques used (Table 2). Dual-phase CT and MRI were done in 14 and 13 patients, respectively. Amongst the 8 patients in whom the former localized the lesion, only 4 also revealed the lesion on MRI. In all the patients in whom insulinoma was localized on MRI, dual-phase CT also revealed an insulinoma. One patient had splenic artery dissection during IADSA; this procedure was discontinued in 2002 because of its invasive nature and development of expertise with IOUS.

**Surgery**

Thirty of 31 patients underwent surgery. Surgery was not done in one patient due to multiple liver metastases. All of the 30 patients were cured of hypoglycemic symptoms after surgery. One subject with previous failed surgery elsewhere underwent Whipple’s resection procedure because of location of tumor in the uncinate process and significant peripancreatic adhesions, which prevented safe enucleation.

**Intra-operative localization**

At surgery, the lesions were detected at inspection in 17 patients and by palpation in 22 patients. IOUS detected tumors in 11 of 12 patients in whom it was done; it was particularly useful in four patients, including 3 with negative pre-operative imaging and one in whom the pre-operatively localized lesion could not be felt at palpation. In one subject, a pre-operatively localized lesion was not identified at IOUS but could be detected by palpation.

Within the pancreas, the tumor was located in the tail region in 15 (48.1%) patients, and in the head and in the body regions in 7 (22.6%) patients each. One patient had tumors in the head and the uncinate process, and another patient had tumors in the head, body and tail regions. The mean tumor size was 1.8 (0.7) cm (range 0.5-3.0).

Peri-pancreatic lymph nodes showed tumor in only one of the 4 patients in whom these were excised; in one subject, tuberculous lymphadenitis was found.

**Intra-operative blood glucose monitoring**

The mean plasma glucose level estimated prior to tumor removal was 129.7 (46.8) mg/dL, and within the first hour after surgical removal of a suspicious lesion was 175.1 (71.4) mg/dL. Four subjects did not show immediate postoperative rebound hypog-
lycemia. In 27 subjects, there was transient postoperative diabetes, with steady drop of blood glucose to normal value by day 6. Two subjects needed long-term insulin. Twenty-nine subjects had no recurrence of hypoglycemia and are considered cured on follow up.

**Histology**

Histological findings were available in 18 of the 30 operated patients. In 15 of these, a neuroendocrine tumor was identified; in 2 of the remaining 3 patients, hypoglycemic symptoms were cured after distal pancreatectomy.

**Discussion**

In patients with suspicion of insulinoma, presence of hyperinsulinemic hypoglycemia should be documented before an attempt at localization is made. In patients with severe and recurrent symptoms, hypoglycemia may occur spontaneously, whereas for patients with milder symptoms a 72-hour fast has been recommended. In our experience, a 48-hour fast was adequate in all patients.

Though our series is small, our experience with various localization techniques was similar to those reported in the literature. In one series of 67 patients, 88% had solitary insulinoma, 4% had multiple tumors, and 6% had islet-cell hyperplasia. In this study, conventional CT successfully localized the tumor in 33%, single-slice helical CT in 58%, multi-detector CT in 100%, MRI in 85% and angiography in 65%, and a combination of available methods achieved a sensitivity rate of 88%. In general, trans-abdominal US and conventional CT perform poorly. As in other studies, our data show that if dual-phase CT does not identify a lesion, conventional MRI is unlikely to be of additional help. As compared to the conventional technique, MRI with special fat-suppression sequences during breath holding has a high sensitivity; this however needs special expertise. Endoscopic ultrasonography and arterial calcium stimulation and venous sampling (ASVS) have been reported to have a sensitivity of 96% in localizing insulinomas; however, we do not have facilities for these.

If pre-operative localization fails, it is prudent to attempt surgery only if facilities for IOUS are available. We consider IOUS mandatory irrespective of pre-operative localization, for two reasons. Firstly, it can help avoid a blind distal pancreatectomy, should no lesion be identified by palpation. Secondly, it may identify additional lesions not demonstrated pre-operatively or intra-operatively by palpation. However, studies have shown that despite all efforts at the best centers, 10% of insulinomas will not be found at surgery.

In conclusion, dual-phase CT is recommended as the imaging of first choice. We consider IOUS mandatory irrespective of pre-operative localization. Every effort should be made to rule out multiple insulinomas intra-operatively by IOUS, than risk surgical failure.

**References**


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**News and Notices**

The 4th S R Naik Memorial Workshop on “Biomedical Research: Methods, Tools and Future” will be organized by the Department of Gastroenterology, SGPGI, Lucknow, September 23 and 24, 2006.

For details contact: Dr Uday C Ghoshal. E-mail: ghoshal@sgpgi.ac.in

A Symposium on Diagnosis and Treatment of Gastrointestinal Infections will be held at the Postgraduate Institute of Medical Education and Research, Chandigarh, January 13 and 14, 2007.

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