INTRODUCTION
Pancreatic neuroendocrine tumors (PETs) are rare lesions with a reported incidence of 4 cases/1 million patient-yr. Insulinomas, the commonest of all PETs, generally present in females between 30-60 years. Most insulinomas are sporadic, solitary and less than 2 cm in diameter. Multiple ones are associated with MEN-I. Pasieka et al reported only 4% larger than 3 cm. Those larger than 3 cm are more likely to be malignant with local invasion or metastases to the peripancreatic lymph nodes and liver.

Here, we are reporting this case because of the unusual large size (11 × 9 cm) without local invasion and metastases treated by enucleation.

CASE REPORT
32-year-old male, a known case of CML on treatment, came with history of recurrent episodes of giddiness since last 4 years, relieved after consumption of sugar.

Clinical examination revealed an ill-defined epigastric lump, firm in consistency. Patient was a diagnosed case of CML and had received hydroxyurea and allopurinol for 5 years followed by Imitinab for 8 months.

On presentation, patient had serum glucose level of 28 mg/dl (1.55 mmol/l) and symptoms of hypoglycemia relieved by IV glucose. Plasma insulin and C-peptide level were significantly elevated. Subsequent biochemical indices obtained during a 20-h fast confirmed the diagnosis of insulinoma. The workup for MEN-1 syndrome was negative. CEA and CA19-9 were normal.

Contrast enhanced CT (CECT) abdomen revealed a 11 × 9.5 × 7 cm lesion involving head and uncinate process of pancreas with no associated lymphadenopathy (Fig. 1).

Plasma insulin 26.6 μU/ml or 186.2 pmol/l (random)
Plasma insulin 11.5 μU/ml (at FBS < 45 mg/dl)
C-Peptide > 7 ng/ml
Se. Prolactin 8.6 ng/ml
Se. Calcium 2.38 mmol/l
Se. Phosphate 3.99 mg/dl

Fig. 1: On venous phase of CT abdomen contrast study, the lesion shows moderate heterogeneous enhancement causing anterior displacement of splenic vein.
MRI contrast study measured a $11.3 \times 9.3 \times 7.7$ cm, soft tissue mass in the uncinate process. Rest of the pancreatic parenchyma showed atrophy and fatty replacement. Despite giant size of the tumor, neither of the imaging modalities showed any local or vascular invasion or liver metastasis.

A provisional diagnosis of insulinoma was made. At exploration using Chevron incision large mass (130 gm) measuring $11 \times 9 \times 7$ cm was seen arising from the uncinate process of pancreas (Fig. 2). Portal vein and CBD were splayed over the tumor. Kocherization done, tumor was dissected free from IVC posteriorly and pancreas, duodenum, portal vein and CBD anteriorly (Fig. 3). There was no evidence of any pancreatic duct communication, gross invasion, abnormal lymph nodes, or liver metastases (Fig. 4). In view of comorbid condition of CML and absence of any pancreatic duct communication, instead of major pancreatic resectional procedure (Whipples) decision to do enucleation was taken. Surgery took 3 hours, blood loss was around 350 ml. The weight of the resected specimen was 130 gm (Fig. 5). No significant postoperative complication occurred. On histopathology tumor was found to be well-differentiated PET-insulinoma of uncertain behavior (WHO criteria >2 cm in size; <2 mitoses/HPF; angioinvasion; >2% Ki-67+ cells) (Fig. 6). On immunohistochemistry, the neoplastic cells were positive for cytokeratin, synaptophysin and chromogranin A.

Postoperatively, the patient reported complete resolution of his symptoms. One month postoperative, his FBG and insulin levels were 120 mg/dl and 5 μU/ml respectively. Follow-up CT at one year was normal.

**DISCUSSION**

In three of the largest reported series, mean tumor size of insulinomas was 1.5 cm with a range of 0.1 to 7.0 cm. In two series, 7.6% and 12% of patients with insulinoma had MEN type I syndrome.
Giant Insulinoma in Uncinate Region Treated by Enucleation

After exhaustive literature search, no association between CML and insulinoma was found. The diagnosis of malignancy is based on the presence of metastases to liver or regional lymph nodes or gross evidence of local invasion. In a review of malignant insulinomas, Danforth et al. identified 62 cases: 17 from the NIH and 45 others reported in the literature. Additional review of the world literature identifies only 3 reported cases of insulinomas more than 9 cm in size, all of which were benign by traditional criteria. The large size and weight of tumor is related to extensive proportion of amyloid. Amyloid deposits have been demonstrated in more than 50% of insulinomas, but not to the extent present in our patient’s tumor.

CT is imaging modality of choice for tumor detection and staging, surgical planning, and follow-up in patients with PETs. Approximately 40% of all insulinomas remain nonlocalized preoperatively, and between 3% and 10% remain occult even after intraoperative palpation and use of intraoperative ultrasound.

Percentage of Ki-67+ cells provides an assessment of tumor’s proliferative index and risk of malignant behavior. The patient’s tumor was classified as insulinoma of uncertain biological behavior according to the 2000 WHO Classification for Pancreatic Endocrine Neoplasms.

No histological criteria/histochemical markers can reliably predict biological behavior, and definitive diagnosis of malignant insulinoma is still based on gross presence of metastases or evidence of local invasion.

Whipple and Franz (1935), described insulinoma triad: symptoms of hypoglycemia, plasma glucose level of 45 mg/dl or less during symptoms of hypoglycemia, and relief of symptoms with administration of glucose. Vezzosi et al emphasized concomitant measurement of C-peptide levels is mandatory for establishing a diagnosis of insulinoma. In most patients with insulinoma, diagnosis is established on supervised fast during which simultaneous measurements of glucose, insulin, and C-peptide are obtained. In those with limited disease, surgery remains primary method of cure. For patients with advanced disease, cytoreductive surgery is recommended for palliation and increased survival.

In conclusion, this case report emphasizes some unusual features of insulinoma of which a clinician should be aware. This includes an extremely large tumor size in absence of definite features of malignancy, the inordinate deposition of amyloid, which accounted for 70% of the tumor volume. The goal of treatment in patient with insulinoma is to identify and excise the primary tumor and all metastatic disease. However, radical excisions are not mandatory in associated comorbid conditions. Follow-up CECT abdomen is recommended for insulinomas of uncertain behavior to evaluate subsequent development of recurrent or metastatic disease.

REFERENCES