Sultan Qaboos University Medical Journal
March 2008, Volume 8, Issue 1, p. 63-67
Sultan Qaboos University©
Submitted - 20th June 2007
Accepted - 14th January 2008

CASE REPORT

Insulinoma: A Rare Cause of a Common Metabolic Disorder - Hypoglycaemia

***Omayma El Shafie,[1] Dilip Sankhla,[2] Nayil Al-Kindy,[3] Aisha Al-Hamadani,[4] Christopher Grant,[3] Nicholas Woodhouse[1]**

الوَرَمُ الجَزيريّ (انسولينوما) : سبب نادر للاضطراب الأيضي (الاسَتقلابي) واسع الانتشار - نقص سكر الدم

أميمة الشافعي، ديليب سانخلا، نايل الكندي، عائشة الحمداني، كريستوفر جرانت، نيكولاس وودهاوز

الملخص: تقرير عن أول حاله في سلطنة عمان لمريض عماني يعاني من الورم الجزيري والذي تم استئصاله مع ذيل غدة البنكرياس بواسطة المنظار. هذه الحالة تثبت أهمية اخذ تاريخ المرض من المريض و/أو عائلته . كما يوضح هذا التقرير أهمية فحص نسبة السكر في الدم للمرضى الذين يعانون من فقدان الوعي المتكرر . وكذلك اخذ عينات دم أخرى للتأكد من نسبة السكر في المعمل ونسبة هرمون الأنسولين وبيبتايد – ج طليع الانسولين ومستويات يوريا السلفونيل - اذا كانت هناك ضرورة لذلك. واذا لم يكن باستطاعة الرنين المغناطيسي تحديد موقع الورم بالضبط . يمكن حينذاك الفحص بتَخْطيطُ الصَّدَى بالتَّنْظيرِ الدَّاخِلِيّ . أو بالتَفَرُّس باستخدام الانديوم الثلاثي الموسوم بالاوكتيروويد لتحديد مكان الورم في البنكرياس اذا استجاب المريض الذي يعاني من انخفاض سكر الدم للعلاج بالاوكتيروويد.

مفتاح الكلمات: بيبتايد - ج . انخفاض سكر الدم . الجراحة بالمنظار . استئصال البنكرياس.

ABSTRACT We describe the first patient diagnosed with an insulinoma in Oman and successfully managed with a distal laparoscopic pancreatectomy. The importance of obtaining a good history from the patient and/or his family is stressed. All patients with loss of consciousness must have a Reflow check carried out and, if hypoglycaemic, this should be documented in the laboratory and a simultaneous serum sample stored for measurement of insulin, C-peptide proinsulin and sulphonylurea levels, if subsequently indicated. If magnetic resonance imaging fails to locate the tumour, endoscopic ultrasound of the pancreas, or indium 111 labelled octreotide scanning is indicated if the patient's hypoglycaemia has previously responded to treatment with octreotide.

Key words: Insulinoma; C-peptide; Hypoglycaemia; Laparoscopy; Pancreatectomy.

Hypoglycaemia is a common metabolic problem and may result from increased peripheral uptake of glucose, failure of glucose production or a combination of both. By far the commonest cause is increased peripheral glucose uptake resulting from stimulation of the insulin receptor (INS-R) by endogenous overproduction or exogenous administration of excess insulin. Rarely, hypoglycaemia is caused by increased circulating levels of molecules resembling insulin such as insulin like growth factors (IGFs) or antibodies directed against the INS-R. Hypoglycaemia also occurs in patients with advanced liver disease resulting from a failure of gluconeogenesis. The role of the kidney is less certain; glucose uptake and synthesis is high normally and renal failure often results in hypoglycaemia. As insulin is degraded by the kidney, hypoglycaemia may in part be due to prolongation of its actions.[1-5]

Hypoglycaemia has a potential for serious neuronal damage and death. The patient described here had recurrent symptoms for two years that were initially thought to result from epilepsy and later a conversion reaction. Insulinoma is rare with an incidence of only 4 per 1 million persons per year, but it is the common-

Departments of [1]Medicine, [2]Radiology and Molecular Imaging, [3]Surgery, [4]Pathology, College of Medicine & Health Sciences, Sultan Qaboos University, Muscat, Sultanate of Oman.

**To whom correspondence should be addressed. Email: omayma0@hotmail.com*

Table 1: ***Simultaneous blood sampling of patient when hypoglycaemic***

Glucose	1.5	(3.5 – 5.0) mm/l
Insulin	9.0	(1.9 – 23) miu/L
C-peptide	2	(1.5 – 4.5) ug/L
Pro-insulin	21	(6.4 – 9.4) pm/l

Table 2: ***Octreotide trial 100 micrograms s/c time 0***

Time (minutes)	-15	0	30	60	120
Glucose mmol/L	1.4	1.7	1.8	1.4	1.0
Insulin mIU/L	2.1	3.4	0.3	1.9	2.0

est cause of hypoglycaemia in otherwise healthy adults who are not taking antidiabetic drugs. The median age is 47 years with a slight female preponderance of 59%. 87% of insulinomas are single benign tumours, 6% are malignant and 7% are multiple benign tumours and associated with multiple endocrine neoplasia type 1 (MEN-1).[1, 2]

CASE REPORT

A 23 year old Omani male had a 2 year history of recurrent loss of consciousness and convulsions.

On the first day of Ramadan (Islamic month of fasting) in 2006, he presented to the Accident and Emergency Department of Sultan Qaboos University Hospital, Oman, with loss of consciousness. His blood glucose was measured by Reflocheck, a blood glucose monitor, and was found to be 1.5mmol/L. On receiving intravenous dextrose, he regained consciousness. He was then discharged with a referral letter to the endocrine clinic. This delayed his admission by two months.

His attacks had started in Ramadan 2005, when he was unable to fast for more than 10 days. A year later in Ramadan 2006, fasting became impossible for more than a few hours hence his hospital visit. The family reported that frequent meals made him less liable to attacks. There was no family history of diabetes and he was not known to have diabetes. His parents and ten siblings were healthy. His physical examination was unremarkable.

He was admitted and started on a 72 hour fast. After 8 hours, his blood glucose fell to 1.5 mmol. (Reflocheck). Blood samples were taken for laboratory confirmation of the plasma glucose, and levels of insulin, C-peptide, pro-insulin and sulphonylureas. The fast was terminated and he was given intravenous glucose. Treatment

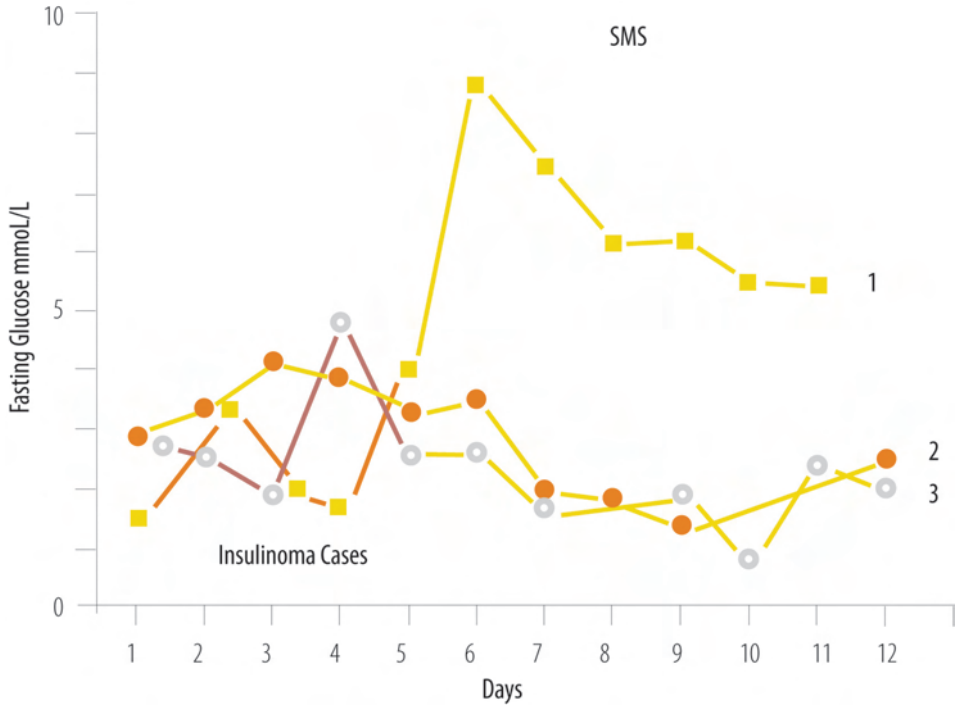

Figure 1: ***A therapeutic trial of octreotide (SMS) in 3 patienrs with insulinomas. Insulin secretion can be inhibited, with normalisation of the blood sugar level, only in those patients whose tumours have receptors for octreotide (<50%). Only patient 1 responded***

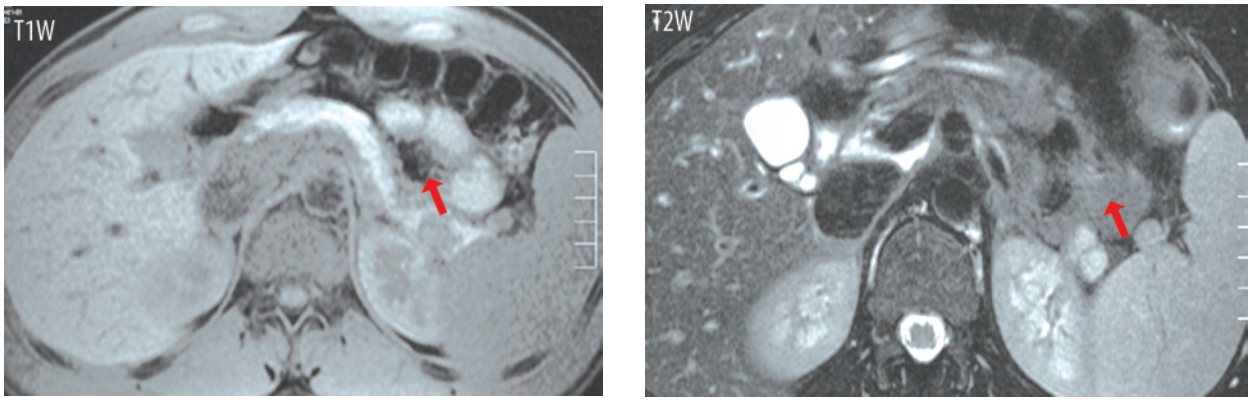

Figure 2: *The Patient's CT scan was normal but an MRI revealed a 1.5 x 2 cm tumour localized in the tail of the pancreas (Arrows)*

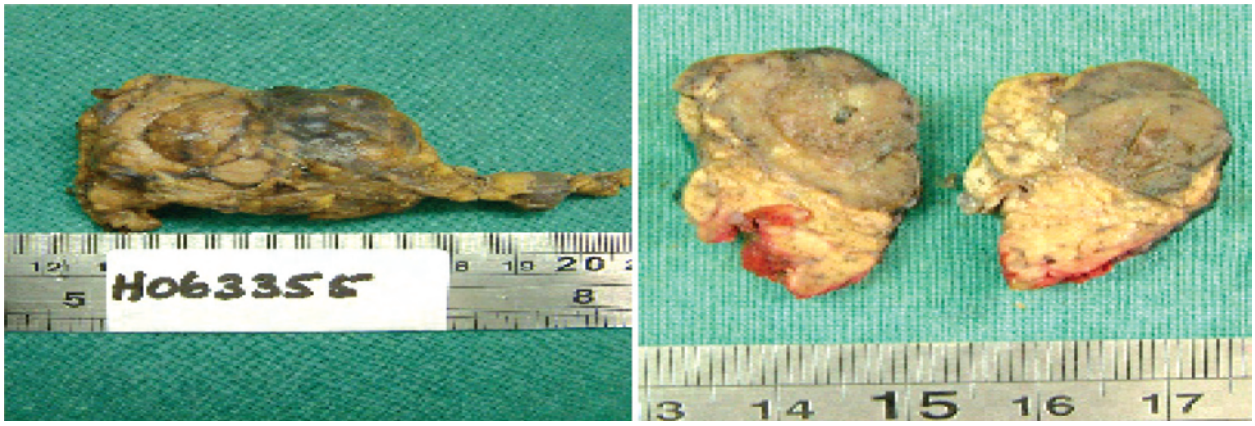

Figure 3: *Patient's pancreatic tumour*

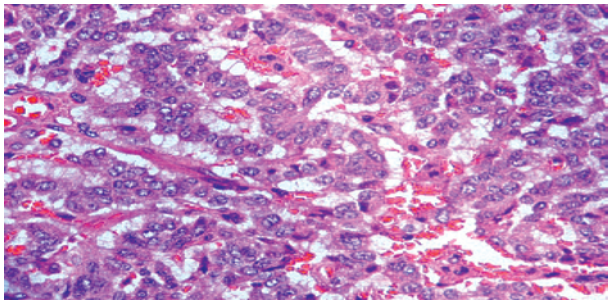

Figure 4: *Microscopic view of tumour*

Table 3: *WHO classification of pancreatic endocrine tumours*

- Well differentiated endocrine tumours
- Well differentiated (low grade maligant) carcinoma with gross local invasion or distant metastasis
- Poorly differentiated endocrine carcinoma small cell neuroendocrine carcinoma

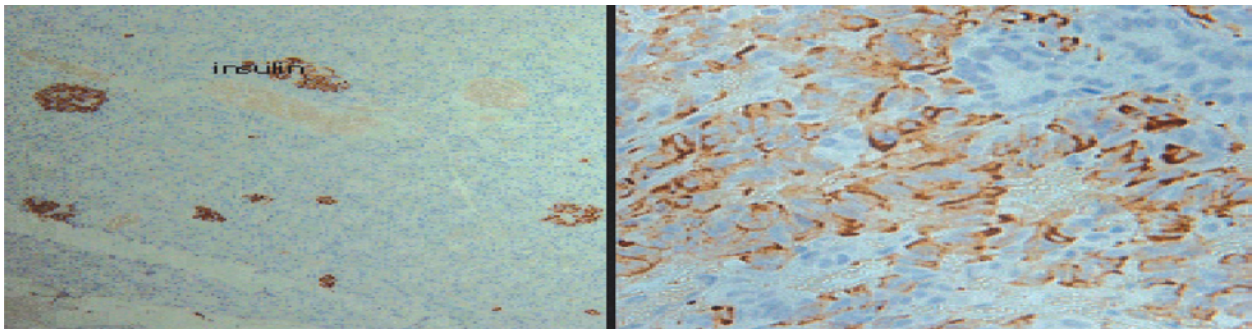

Figure 5: *Insulin staining. On left normal staining, on right patient's tumour*

Table 4: ***Characteristics of well differentiated endocrine tumours***

Benign	**Uncertain behaviour**
- No extrapancreatic spread - No vascular invasion <2cm - <2 mitoses/10HPF - <2% ki-67 positive cells	- No extrapancreatic extension - BUT with one or more of these features: >2cm in size angioinvasion >2% ki-67 positive cells

was started with diazoxide 50 mg three times a day, and thereafter he remained asymptomatic.

The results in Table 1 show an inappropriately high insulin concentration for the level of blood glucose. The detectable C-peptide excludes the injection of exogenous insulin as commercial insulins contain no C-peptide.[1, 2] Sulphonylurea was not detected. These results confirm excessive and inappropriate endogenous insulin overproduction. Normally, circulating proinsulin levels account for less than 22% of the serum insulin value, but the ratio of more than 24% is seen in 90% of all insulinomas when greater than 40% malignancy is usually indicated. Our patient's value was more than 50% and he has to be carefully followed up. An octreotide trial [Table 2] produced no significant change in blood glucose or insulin levels and therefore an octreotide scan was not done. Only 50% of insulinomas have octreotide receptors and in these cases the drug can be used therapeutically[6] [Fig 1] or to locate the tumour by scanning with indium III labelled hormone.

Two weeks later, he was admitted for further assessment. There had been no attacks of hypoglycaemia since starting on diazoxide. He underwent laparoscopic distal pancreatectomy[7] and the tumour was localized by intraoperative laparoscopic ultrasound during surgery.[8] The surgery was uneventful and the histopathology confirmed an insulinoma [Figs. 4-5] of "uncertain behaviour" by WHO classification [Tables 3 & 4].

Since surgery, the patient has been very well with no hypoglycaemic attacks and he is looking forward to the next Ramadan moon to undertake his fast.

DISCUSSION

This case illustrates the necessity of good history taking. The patient's symptoms very clearly improved by taking food. The family gave a vivid description of how he was often too weak to walk to the table for his meals. He would sometimes sink to the ground and the family would restore him by bringing food to him. During Ramadan, by midday, he would be weak and confused until breaking his fast. Hypoglycaemia was not, however, suspected and he was referred to neurology and psychiatric clinics. In the Mayo Clinic series of 224 cases of insulinoma as many as 20% of patients had been misdiagnosed as having neurological or psychiatric disorders.[2]

In this article, we have outlined a systematic approach to the investigation and management of patients with spontaneous hypoglycaemia.[9] The largest series in the literature is from the Mayo Clinic[2] where, in an 80-year period, 224 cases were seen. 87% were benign tumours, 6% were malignant, and 7% were associated with MEN-1. Their follow up shows a higher recurrence rate in patients with MEN-1 [Figure 6]. Patients with benign insulinomas had a survival rate which did not differ from that expected in the general population. This is not the case in those with malignant insulinomas [Figure 7].

MEN-1 is excluded in our patient as the pituitary CT scan and bone profile were normal. He is now free of symptoms since surgery done in November 2006. In the Mayo Clinic series, a cure has been defined as being totally free of symptoms for 6 months after removal of the insulinoma.[2]

The next Ramadan fast will be used to confirm the success or otherwise of his treatment.

CONCLUSION

The symptoms of hypoglycaemia may include loss of consciousness, convulsions and personality changes. In such a patient, hypoglycaemia should be looked for and, if found by Reflocheck, two venous samples must be taken immediately; one for laboratory confirmation of the glucose and insulin level and the other stored for C-peptide, pro-insulin and sulphonylurea measurement, if indicated. This must not delay the administration of intravenous glucose, which should be given without awaiting a result. If in such a patient hypoglycaemia is found by finger prick sampling, it is essential to take two venous samples immediately. One sample should

be taken for laboratory confirmation of the glucose and insulin levels. The other should be stored for other possible investigations (C-peptide, pro-insulin and sulphonylurea). You should then take a history from your recovering patient.

REFERENCES

1. Siperstein A, Clark OH, Rushakoff RJ. Tumor Syndromes: Insulinoma and other Hypoglycemias. In: Goldine ID, Rushakoff RJ, eds. Diabetes and Carbohydrate Metabolism. From http://www.endotext.org/diabetes/index.htm. Accessed June 2007.

2. Service FJ. Diagnostic Approach to Hypoglycemia in Adults. From http://www.uptodate.com. Accessed June 2007.

3. Service, FJ. Hypoglycemic disorders. N Engl J Med 1995; 332:1144-1152.

4. Vortmeyer AO, Huang S, Lubensky I, Zhuang Z. Non-islet origin of pancreatic islet cell tumours. J Clin Endocrinol Metab 2004; 89:1934-1938.

5. Minn AH, Kayton, M, Lorang, D, et al. Insulinomas and expression of insulin splice variant. Lancet 2004; 363:363-367.

6. Romeo S, Milione M, Gatti A, Fallarino M, Corleto V, Morano S, et al. Complete Clinical Remission and Disappearance of Liver Metastases after Treatment with Somatostatin Analogue in a 40-Year-Old Woman with a Malignant Insulinoma Positive for Somatostatin Receptors Type 2. Horm Res 2006; 65:120-125.

7. Ayav A, Bresler L, Brunaud L, Boissel P, SFCL (Société Française de Chirurgie Laparoscopique), AFCE (Association Francophone de Chirurgie Endocrinienne). Laparoscopic approach for solitary insulinoma: a multicentre study. Langenbecks Arch Surg 2005; 39:134-140.

8. Mirallie E, Pattou F, Malvaux P, Filoche B, Godchaux JM, Maunoury V, et al. Value of endoscopic ultrasonography and somatostatin receptor scintigraphy in the preoperative localization of insulinomas and gastrinomas. Experience of 54 cases. Gastroenterol Clin Biol 2002; 26:360.

9. Hirshberg B, Livi A, Bartlett DL, Libutti SK, Alexander HR, Doppman JL, et al. Forty-eight-hour fast: The diagnostic test for insulinoma. J Clin Endocrinol Metab 2000; 85:3222-3226.