Insulinoma Induced Hypoglycaemia in a Jamaican Patient

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ABSTRACT

Herein reported is the case of a young woman who had hyperinsulinaemic hypoglycaemia which was biochemically consistent with an insulinoma. Initial imaging was negative and definitive treatment was delayed until repeat imaging localized the tumour several years later. This case demonstrates the importance of clinical judgment and biochemical testing in the diagnosis of insulinoma despite negative imaging.

Hipoglicemia Inducida por Insulinoma en un Paciente de Jamaica

RESUMEN

Aquí se reporta el caso de una joven que presentó hipoglicemia hiperinsulinémica, bioquímicamente concordante con un insulinoma. La imagen inicial fue negativa y el tratamiento fue retardado hasta que mediante la repetición de la técnica de imaginología años más tarde localizó el tumor. Este caso demuestra la importancia de juicio clínico y las pruebas bioquímicas en el diagnóstico del insulinoma, especialmente frente a la obtención de una imagen negativa.

INTRODUCTION

Insulinomas are relatively rare pancreatic endocrine tumours with an estimated incidence of 4 cases per million a year (1). Most insulinomas are solitary and benign, however up to 10% may be malignant. Malignant insulinomas tend to occur more frequently in patients with multiple endocrine neoplasia Type-1. Patients with insulinomas usually present clinically with symptoms of fasting hypoglycaemia as a result of inappropriate insulin secretion. The authors report a case of insulinoma in which an early biochemical diagnosis was made, but definitive treatment was delayed due to negative preoperative localization.

CASE REPORT

A 34-year old Afro-Jamaican woman was seen in the Endocrinology Clinic of the University Hospital of the West Indies (UHWI) for evaluation of hypoglycaemia. She had recurrent episodes of generalized weakness, tremulousness and dizziness for six years. These symptoms occurred sever-

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al times per day and were typically relieved with food. In order to minimize these episodes, the patient altered her eating habits, consuming up to eight meals during the day and also awoke several times throughout the night to eat. This resulted in significant weight gain over the six-year period. The patient had no medical illnesses and was previously well. She worked in a fast food restaurant and lived with her mother who was being treated with glyburide and metformin for Type-2 diabetes mellitus. She had no personal or family history of nephrolithiasis, fractures, pituitary tumours or other features suggestive of multiple endocrine neoplasia Type-1.

Physical examination revealed a healthy-appearing female who was overweight (BMI 29.1 kg/m²). She did not have acanthosis nigricans and had no peripheral stigmata of chronic renal or liver disease.

In order to confirm the presence of fasting hypoglycaemia and to determine its aetiology, the patient was admitted to hospital for a supervised 72-hour fast. On presentation to hospital (after an overnight fast of approximately 11 hours), she was experiencing neuroglycopaenic and neurogenic symptoms. At that time, a glucometer reading was 1.8 mmol/L. Venous blood samples were taken and 50% dextrose was then administered intravenously with immediate resolution of symptoms, thus fulfilling Whipple's triad. The laboratory testing confirmed hyperinsulinaemic hypoglycaemia and a sulphonylurea screen was negative (Table

1). Proinsulin and ß-hydroxybutyrate tests were unavailable. The results of liver, renal and thyroid function tests were

Table 1:   Results at termination of supervised fast (UHWI)

	Result	Normal range
Fasting glucose (mmol/L)	2.0	< 6.1
Insulin (uIU/ml)	45	6 – 27
C-peptide (pmol/L)	1026	298 – 1324
Chlorpropamide	None detected	–
Tolazamide	None detected	–
Tolbutamide	None detected	–
Glyburide	None detected	–
Glipizide	None detected	–
Acetohexamide	None detected	–

normal and she had a normal cortisol response to a short 250-mcg ACTH stimulation test.

Based on these biochemical findings, the patient was diagnosed with an insulinoma. Abdominal imaging with computed tomography (CT) and magnetic resonance imaging (MRI) with gadolinium failed to demonstrate a pancreatic mass, so surgery was not performed. She continued to be followed in the Endocrinology Clinic and was subsequently referred to the National Institutes of Health (NIH) five years after the initial diagnosis for tumour localization and surgery.

At the NIH, the patient underwent supervised fasts on consecutive days, the results of which are shown in Table 2.

Table 2:   Results of supervised fasts (NIH)

	Day 1		Day 2	
	Start	End	Start	End
Glucose (mmol/L)	3.1	1.3	3.8	1.2
Insulin (uIU/ml)	127	212	56.2	63
C-peptide (pmol/L)	2286	2352	1789	1789

During the first fast, she experienced symptomatic hypoglycaemia after two hours with venous glucose 1.3 mmol/L, insulin 212 uIU/ml, C-peptide 2352 pmol/L and proinsulin 0.75 ng/mL. This unusually high fasting insulin concentration raised the suspicion of factitious hypoglycaemia due to exogenous insulin administration or sulphonylurea use. A sulphonylurea screen was negative and the patient denied insulin use. During the second fast, she became symptomatic after 12 hours with venous glucose 1.2 mmol/L, insulin 63 uIU/ml and C-peptide 1789 pmol/L. These results were consistent with endogenous hyperinsulinism secondary to an insulinoma and preoperative localization was undertaken. Imaging studies performed included an abdominal CT scan (Fig. 1) which showed a 2.9 cm hypervascular mass in the body of the pancreas and MRI which showed a contour bulge in the same area. Calcium-stimulated angiography (Fig. 2) was then performed, showing a 'step-up' in the proximal splenic artery and the superior mesenteric artery suggestive of a lesion in the head or neck of the pancreas.
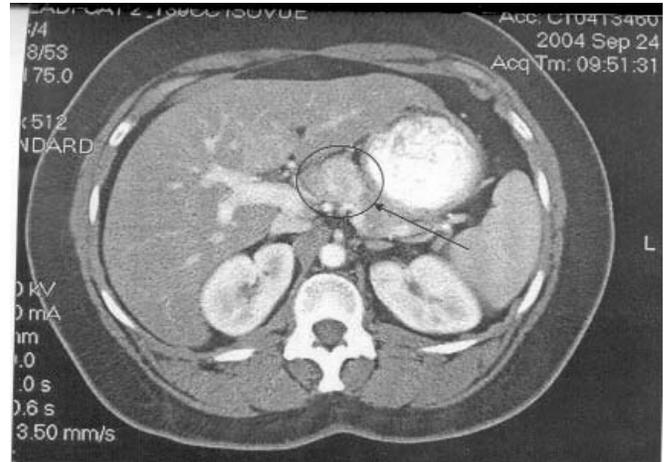

Fig. 1:   Abdominal computed tomography scan showing a 2.9 cm hypervascular mass in the body of the pancreas.
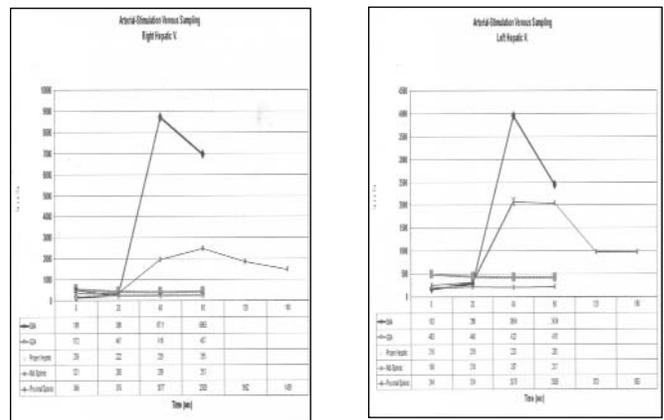

Fig. 2:   Calcium-stimulated angiogram showing a 'step-up' in the proximal splenic artery (Fig. 2a) and the superior mesenteric artery (Fig. 2b).

At surgery a 1.8 x 1.5 cm mass was noted at the neck of the pancreas. Distal pancreatectomy was performed. A neuroendocrine tumour was confirmed on frozen section and immunohistochemistry was positive for glucagon, insulin, chromogranin and synaptophysin and focally positive for somatostatin (Fig. 3a–3c).
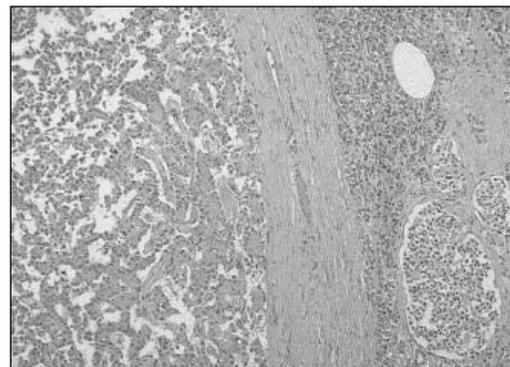

Fig. 3a: The islet cell adenoma at the left contrasts with the normal pancreas with islets at the right.
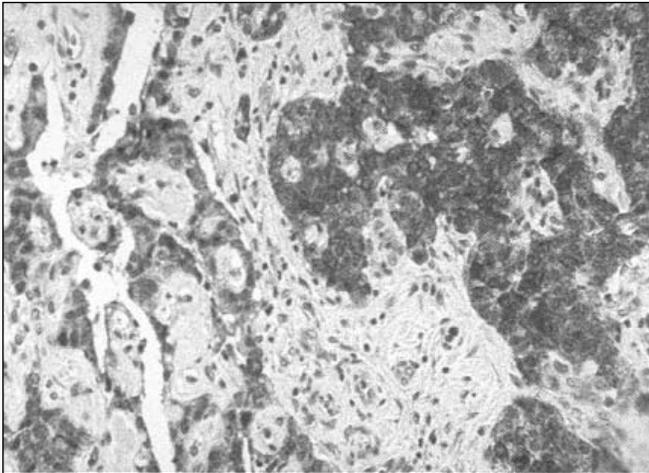
Fig. 3b: Immunohistochemical stain for insulin in the insulinoma (insulin stains brown).
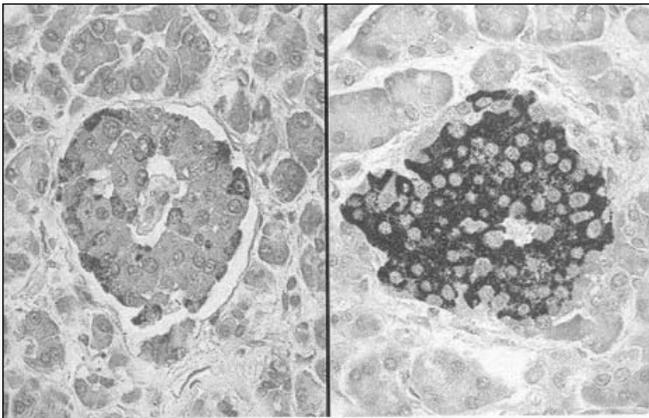

Fig. 3c: Immunoperoxidase staining: on the right, antibody to insulin, on the left, antibody to glucagon.

Postoperatively, the patient developed hyperglycaemia (glucose 13.9 – 16.7 mmol/L) requiring insulin therapy, initially by intravenous infusion and then by subcutaneous injections. She was discharged from the NIH on 10 mg glyburide daily.

On her return to Jamaica, she implemented healthy lifestyle changes (avoiding sweets and fatty food, doing regular exercise), resulting in significant weight loss. The glyburide was discontinued after two months. At her most recent evaluation, her BMI was 20.7 kg/m^2, HbA1c 5.9% and fasting glucose 5.2 mmol/L. She had impaired glucose tolerance on an oral glucose tolerance test. At the time of writing, 12 months after surgery, she has continued to remain free of hypoglycaemic symptoms.

DISCUSSION

The diagnosis of insulinoma is based on Whipple's triad *ie* typical symptoms of hypoglycaemia induced by fasting, demonstration of hypoglycaemia (*ie* plasma glucose # 2.8 mmol/l) at the time of symptoms and prompt reversal of

symptoms after glucose administration, in the presence of inappropriately high or normal insulin, proinsulin and C-peptide (2).

The supervised 72-hour fast is the gold standard test for the diagnosis of insulinoma. The test is necessary to document hypoglycaemia and its relationship to the patient's symptoms, as well as to demonstrate inappropriate insulin concentration in the face of hypoglycaemia. Levels of plasma glucose, insulin, C-peptide and proinsulin are measured simultaneously at baseline and at intervals throughout the fast (Table 3). The fast should be terminated when patients

Table 3:   Diagnosis interpretation of the results of a 72-hour fast

Diagnosis	Insulin	C-peptide	Proinsulin	Sulphonylurea in plasma or urine
Exogenous insulin	↑↑	↓	↓	–
Insulinoma	↑	↑	↑	–
Sulphonylurea use	↑	↑	↑	+

↑ = increased;   ↓ = decreased

have symptoms or signs of hypoglycaemia and simultaneously have fasting glucose in the hypoglycaemic range (# 2.8 mmol/L). At the end, the plasma levels of glucose, insulin, C peptide, proinsulin, ß-hydroxybutyrate and sulphonylurea are measured. Details of the standardized protocol are available in reviews (3).

It has been proposed that the 48-hour fast should replace the 72-hour fast as the new diagnostic standard (4). In a retrospective analysis of data from 127 patients with insulinoma, 120 (94.5%) had their fasts terminated by 48 hours. Seven patients were fasted beyond 48 hours. Re-evaluation of the data from their fasts revealed that these seven patients actually had subtle neuroglycopaenic symptoms and glucose and insulin concentrations diagnostic of insulinoma by 48 hours and could have had earlier termination of their fasts. Hirshberg *et al* concluded that with the currently available insulin and proinsulin assays, the diagnosis of insulinoma can be made within 48 hours (4). Our patient was hypoglycaemic prior to the beginning of the first test and when tested at each of the subsequent occasions became hypoglycaemic within 2 and 12 hours of beginning the fast.

An important differential diagnosis for insulinoma is factitious hypoglycaemia due to oral hypoglycaemic agents as both have elevations of insulin and C-peptide. A sulphonylurea screen is thus essential to differentiate sulphonylureainduced hypoglycaemia from that due to insulinoma. However, current sulphonylurea assays fail to detect the new generation sulphonylureas (*eg* glicazide, glimepiride) and non-sulphonylurea hypoglycaemic agents (*ie* nateglinide, repaglanide). There have been at least two published case reports in which patients had elevated insulin and C-peptide

levels, and negative sulphonylurea screens but were subsequently found not to have insulinomas. The underlying problem was factitious hypoglycaemia due to repaglinide in one case (5) and glimepiride in the other (6).

The possibility of factitious hypoglycaemia was considered in this patient due to unusually high fasting insulin levels. It was unlikely that she was surreptitiously using exogenous insulin since she did not have the typical suppression of C-peptide levels (7). Sulphonylurea screens were negative on repeated occasions, but as discussed previously she could still have been using newer insulin secretagogues. Proinsulin is not usually suppressible in patients with insulinoma, but is suppressible in non-insulinoma patients at the end of the diagnostic fast (4). Consequently, our patient's marked, non-suppressible hyperproinsulinaemia (proinsulin of 0.75ng/mL, normal, 0–0.2) was in keeping with insulinoma rather than factitious hypoglycaemia. The reason for the unusually high fasting insulin is still not clear. One possible explanation is that there was some degree of insulin resistance (resulting from weight gain) which contributed to the high fasting insulin level at baseline.

The reliability of the biochemical data in the diagnosis of insulinoma is extremely important, because of the relative ineffectiveness of non-invasive tumour localization techniques, as discussed later. Evaluation of retrospective biochemical data from 46 cases of histologically confirmed insulinoma showed that the insulin concentrations alone were equivocal in 17% of cases (8). The addition of C-peptide values clarified the diagnosis in about 50% of the borderline cases, whilst ketone (ß-hydroxybutyrate) concentrations were low during the prevailing hypoglycaemia in all cases. The combination of the three tests was suggested as the most effective method for the biochemical diagnosis of hypoglycaemia due to insulinoma (8). An increased percentage of the proinsulin-like component (%PLC) and proinsulin are characteristic of insulinomas. The older and more cumbersome method, the %PLC, expresses proinsulin values as a per cent of the total immunoreactive insulin when each component is measured against an anti-insulin antibody. The newer and less cumbersome method is to measure proinsulin directly (9). In a series of 98 patients with proven insulinoma, it was found that 85 patients (87%) had proinsulin $ 0.2 ng/ml (10). Proinsulin measurement is especially useful in making a diagnosis of insulinoma when the tumour retains some residual sensitivity to glucose and the insulin levels may become suppressed during hypoglycaemia. Proinsulin should ideally be measured at the beginning and the termination of the fast (9).

Once the biochemical diagnosis of insulinoma is established, localization of the tumour is the next step; this may be done preoperatively or intra-operatively. Preoperative localization modalities include selective arteriography, ultrasound, transgastric endoscopy, CT, magnetic resonance imaging (MRI), radionuclide scanning, transhepatic venous catheterization and calcium-stimulated angiography with catheterization of hepatic veins.

Despite the many attempts aimed at localizing insulinomas, these tumours remain undetected in approximately 40% of patients (11). The need for accurate preoperative localization is a matter of debate. Boukhman *et al* evaluated the sensitivities of tumour localization with various techniques (12). The sensitivities of tumour localization with arteriography, CT, preoperative ultrasonography, MRI, MRI with gadolinium contrast, transhepatic venous sampling, intra-operative palpation of the pancreas and intra-operative ultrasonography were 47%, 24%, 50%, 30%, 40%, 55%, 76% and 91% respectively. Intra-operative ultrasound was therefore more sensitive than pre-operative and other intra-operative techniques for localizing insulinoma. Boukhman *et al* concluded that the currently available pre-operative localization tests are not reliable enough to be recommended when intra-operative ultrasonography is available.

However, most centres recommend some kind of preoperative imaging in order to minimize and guide the surgical intervention, and to disclose cases of multiple tumours or metastatic disease (13). In a series of 25 patients with surgically proven insulinomas, selective intra-arterial calcium stimulation with hepatic venous sampling was the most sensitive of the preoperative localizing studies (88%) (14). Additional C-peptide gradients may also be helpful in assessing the location of a tumour (15). The initial imaging studies for our patient (CT and MRI abdomen) were negative for a pancreatic mass lesion. Repeat CT and MRI at the NIH did reveal the tumour, however this was done five years after the initial study. While it is well known that these modalities are operator and equipment-dependent, and are expected to have a higher yield in a highly specialized centre, the five years time lapse could have resulted in significant growth of an initially small undetectable tumour to within the limits of detection. Preoperative localization with selective intra-arterial calcium stimulation was successful in this case.

In conclusion, the diagnosis of insulinoma is based on clinical suspicion and biochemical testing. Surgery should not be delayed in the patient with negative imaging studies as the best means of tumour localization is with intra-operative ultrasound.

ACKNOWLEDGEMENTS

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