

Hypoglycaemia from Islet Cell Hyperplasia and Nesidioblastosis in a Patient with Type 2 Diabetes Mellitus—A Case Report

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Abstract

Introduction: We report the first case of hypoglycaemia from beta cell hyperplasia with nesidioblastosis in an Asian adult with pre-existing type 2 diabetes. **Clinical Picture:** A 57-year-old Chinese woman presented with hyperinsulinaemic hypoglycaemia despite discontinuation of oral hypoglycaemic agents 4 months after diagnosis of type 2 diabetes. Preoperative portal venous sampling suggested regionalisation to the neck of the pancreas. Intraoperative ultrasound and palpation of the fully mobilised pancreas were non-localising. **Treatment:** A subtotal 85% pancreatectomy was performed with success. **Outcome:** Histology showed no evidence of tumour, but revealed islet hyperplasia and nesidioblastosis. Her diabetes was subsequently well controlled on metformin therapy. **Conclusion:** Endogenous hyperinsulinism from beta cell hyperplasia with nesidioblastosis may rarely occur in type 2 diabetics. However, this remains a diagnosis of exclusion that is confirmed only on surgical pathology. In affected individuals, preoperative portal venous sampling may be falsely localising, especially if selective sampling of the smaller peri-pancreatic veins is omitted. Definite treatment involves pancreatectomy, although the extent of surgical resection is not well established.

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Case Report

A 57-year-old woman was admitted to our hospital for perforated left tubo-ovarian abscess and found to have newly diagnosed diabetes with an admission blood glucose of 23 mM and glycated haemoglobin value of 12% (reference range 4.6% to 6.4%). She denied past symptoms of thirst, polyuria or polydipsia. She had lost a few kilograms in weight over one year which she attributed to her exercise programme. There was no family history of diabetes. On physical examination, she was moderately overweight [weight 73 kg, height 160 cm, body mass index (BMI) 28.5 kg/m²] and was found to be hypertensive (blood pressure 180/

100 mmHg). There was no clinical evidence of diabetic micro-vascular complications. She underwent emergent left salpingo-oophorectomy and was discharged after 10 days on glibenclamide 10 mg b.i.d, metformin 500 mg t.i.d. and nifedipine long-acting 30 mg om. On review 2 months later, her glycaemic control improved drastically with pre-breakfast home glucometer values of 2.7 to 5.0 mM, although she had no symptoms. Her glibenclamide dose was reduced to 10 mg om. A month later, she complained of giddiness with exercise. Because her symptoms persisted despite further reduction in dosage of her oral hypoglycaemic medications, they were stopped completely

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4 months after diagnosis of diabetes. Despite not being on hypoglycaemic therapy for 3 weeks, she continued to develop almost daily episodes of blurred vision, peri-oral and hand numbness and fainting spells (home glucometer values ranged from 2.1 to 3.3 mM) that were relieved by glucose tablets and fruit juices. Her glycated haemoglobin (HbA1c) value was remarkably good at 5% (N: 4.6% to 6.4%). These episodes occurred in the early morning around 0400 to 0500 hours and more than 2 hours post-prandially.

An overnight fast documented unequivocal hypoglycaemia 2.2 to 2.7 mM with inappropriately high circulating insulin (11 to 25 mU/L) and C-peptide (3.3 to 4.5 µg/L) levels. Urine analysis for sulphonylureas (chlorpropamide, gliclazide, tolazamide, tolbutamide) were negative. The raised C-peptide and undetectable sulphonylurea confirmed the presence of endogenous hyperinsulinism causing hypoglycaemia. Serum calcium was normal. A 3-phase spiral computerised tomography (CT) examination of the pancreas using 3-mm sections showed no focal lesions in the pancreas or liver. Because of her frequent symptomatic hypoglycaemic episodes, she was started on diazoxide 100 mg t.i.d. This was increased to 100 mg q.i.d. with improvement in her home glucose monitoring profile (4 to 11 mM) and abatement of her symptoms. As she developed lower limb and facial swelling, she was prescribed hydrochlorthiazide 25 mg b.i.d. and SpanK 0.6 g b.i.d. to counteract the salt-retaining effect of diazoxide.

As her CT pancreas was inconclusive, percutaneous transhepatic portal venous sampling was performed 3 weeks later, after stopping diazoxide for 3 days. During the procedure, she required a 10%-dextrose slow drip to avoid hypoglycaemia. Twelve samples were taken, and the results showed a step-up of insulin concentration at the junction of the inferior mesenteric vein with the splenic vein (Fig. 1). She was discharged uneventfully on the same dose of diazoxide.

She was readmitted 2 weeks later for surgical exploration and excision of presumed pancreatic insulinoma. At pancreatic exploration, the whole pancreas was mobilised and seemed grossly normal with no visible or palpable lesion. Intraoperative ultrasound using a 7 MHz probe (Toshiba SSA-270A/H&G) did not reveal any definite discrete sonolucent mass nor a sonolucent rim around an isodense mass characteristic of an insulinoma. As preoperative portal venous sampling suggested regionalisation of the suspected lesion to the neck of pancreas, a subtotal 85% pancreatectomy was performed. The pancreas was transected 1 cm to the right of the superior mesenteric vein-portal vein axis, and the spleen preserved. Her capillary glucose monitoring results rose

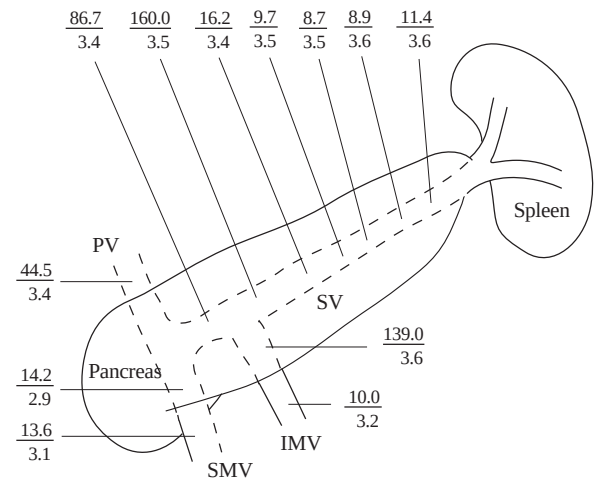


Fig. 1. Percutaneous transhepatic portal venous sampling showing a step up in insulin concentration at the junction of the inferior mesenteric vein with the splenic vein.

Upper number: insulin concentration (mU/L)
Lower number: glucose concentration (mM)

IMV: inferior mesenteric vein
SMV: superior mesenteric vein
SV: splenic vein
PV: portal vein

from 3 to 4 mM preoperatively to 10 to 17 mM postoperatively while on an intravenous 5% dextrose drip. Plasma glucose on the first postoperative day was 11.5 mM, with a corresponding insulin level of 8.3 mU/L. She was discharged on the twelfth postoperative day with metformin 850 mg t.i.d. for control of her diabetes. Follow-up 6 months after surgery showed pre-prandial glucometer values of 5.3 to 8.7 mM, average 6 mM, and HbA1c 6% while on metformin therapy. She remains well with no further recurrence of hypoglycaemic episodes.

Gross examination of multiple sections of the pancreas, which measured 18 x 4 x 3 cm, showed no evidence of tumour. Multiple blocks were taken for histology. Sections were stained for H and E, and immunohistochemically for insulin, glucagon, somatostatin, and chromogranin using the ABC method (Dakopatt) with tissue from pancreas (insulin, glucagon, gastrin, somatostatin), pheochromocytoma (chromogranin) and gut (serotonin) as positive controls. This revealed an increase in the number of islets of Langerhans (Fig. 2). The distribution, however, was uneven, being more concentrated in some areas of the pancreas than others. Clusters of islets in a fibrous stroma without exocrine glands were also noted in the peri-pancreatic fat (Fig. 3). There was considerable variation in the size and shape of the islets. Some were round while others were elongated or irregular in shape measuring from 25 to 400 µm in diameter. Immunohistochemically the islet-cells were stained extensively and intensely for insulin (+++). In addition, single insulin-positive cells were identified among the cells lining the acini and ductules

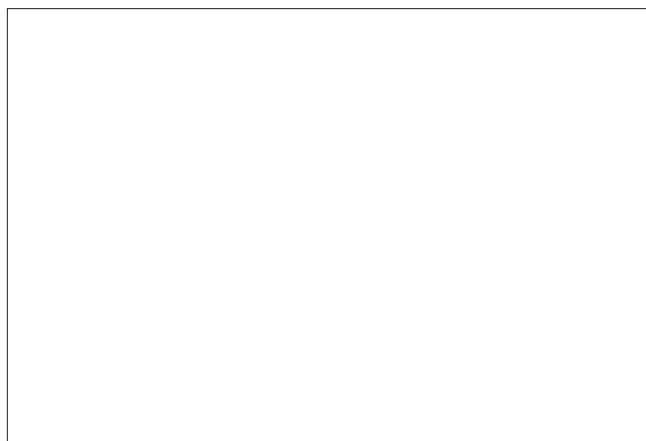


Fig. 2. Section shows pancreas with an increase in the number of islets of Langerhans. There is considerable variation in the size and shape of the islets. Single insulin-positive cells are also seen lining an acinus (arrows). (Immunoperoxidase stain for insulin x50)

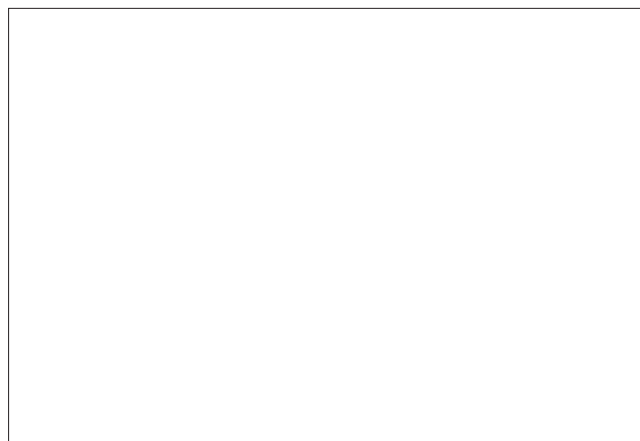


Fig. 4. Section shows an islet of Langerhans in fibrous septum surrounded by ductules. Single insulin-positive cells are identified in the lining cells of the ductules (arrowed). (Immunoperoxidase stain for insulin x250)

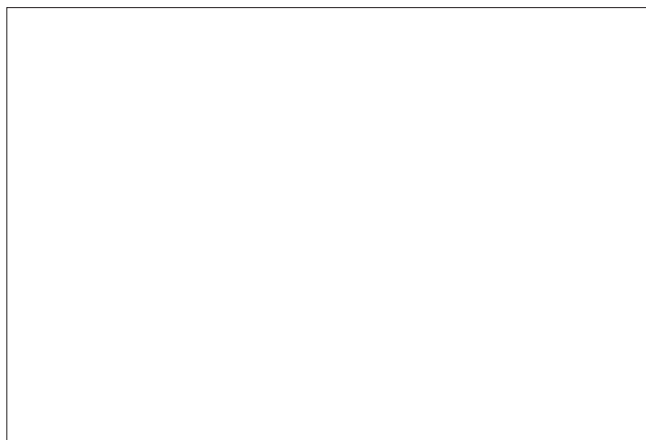


Fig. 3. Clusters of islet-cells are seen in the peripancreatic fat. (H & E x250)

(Fig. 4). Some of the cells in the islets were also positive for chromogranin (++), glucagon (+), somatostatin (+), and gastrin (+) but negative for serotonin. The histological features were consistent with those of islet-cell hyperplasia and nesidioblastosis.

Discussion

The development of endogenous hyperinsulinism with hypoglycaemia in patients with known diabetes is extremely rare. Since the first case was described in 1932, only a handful of cases have been reported in the literature.¹ Most of these cases were due to benign insulinoma, a few were due to islet carcinoma and in only 3 patients islet hyperplasia with nesidioblastosis was found.¹⁻³ The clinical characteristics, histology, management and outcome of these 3 patients, together with our patient, are summarised in Table I. Three patients had type 2 diabetes, and 1 patient with morbid obesity was labelled as being insulin dependent because of diabetic ketoacidosis at onset of diagnosis, and

subsequently required high doses of insulin.² This patient weighed 125 kg when he developed diabetes presenting as diabetic ketoacidosis, with a history of marked weight gain before and after diagnosis of diabetes. All 4 patients had hypoglycaemic symptoms lasting 2 to 3 months, including the 1 to 2 months when anti-diabetic medications were discontinued.

To our knowledge, our patient is the first reported case of islet-cell hyperplasia and nesidioblastosis associated with endogenous hyperinsulinaemic hypoglycaemia in an Asian adult with type 2 diabetes. In contrast to the previous 3 reported cases who had diabetes for several years before the onset of hypoglycaemia, our patient is remarkable in that she developed hyperinsulinaemic hypoglycaemia within 4 months of diagnosis of diabetes. Although the number of cases is small, the data suggest that diffuse islet hyperplasia and nesidioblastosis associated with hypoglycaemia can occur in diabetics who were either on insulin or sulphonylurea, and tends to occur in overweight or obese diabetics. As expected, intraoperative palpation or ultrasound scan were non-localising in all 4 patients. Unlike the case reported by Espinosa-de-los Monteros,¹ we were unable to identify adenomatosis, however the finding of extra-acinar islets situated in fibrous stroma or peripancreatic fat as observed by Bell et al,² was also present in our patient (Fig. 3).

Nesidioblastosis has traditionally been attributed as the commonest cause of endogenous hyperinsulinism in neonates and infants, but is extremely rare in adults. There have been only 3 reported cases occurring in adult diabetics as discussed above. The term “nesidioblastosis” was originally coined by Laidlaw in 1938 as a “diffuse proliferation of islet cells arising from pancreatic ducts or ductules”.⁴ From its original description to mean endocrine cells in close contact with ducts, it was more broadly

TABLE I: REVIEW OF CASES OF HYPOGLYCAEMIA AND ENDOGENOUS HYPERINSULINISM ASSOCIATED WITH ISLET HYPERPLASIA/NESIDIOBLASTOSIS COMPLICATING DIABETES MELLITUS

Ref.	Age (y)/ Sex	BMI (kg/m ²)	Duration of diabetes	Prior anti-diabetic medication	Preoperative	Surgery	Histology	Post-surgical outcome
1	30/F	30	7 years	Glibenclamide	Ultrasound and CT scan non-localising	Subtotal pancreatectomy	Islet hyperplasia, nesidioblastosis, adenomatosis, no nuclear pleiomorphism	At 4 months: diabetes on diet control
2	50/M	125 kg	8 years	Insulin	Coeliac-axis angiogram- blush in tail of pancreas	Subtotal pancreatectomy	Islet hyperplasia, nesidioblastosis, nuclear pleiomorphism	At 6 months: normoglycaemia
3	59/M	*	5 years	Chlorpropamide, then insulin for 5 weeks	Nil	2/3 of pancreas removed	Islet hyperplasia, nesidioblastosis areas of scattered chronic pancreatitis	At 1 year: diabetes on insulin
Present case	57/F	28.5	7 months	Glibenclamide, metformin	CT pancreas non-localising portal venous sampling-insulin gradient at neck of pancreas	Subtotal (85%) pancreatectomy	Islet hyperplasia, nesidioblastosis	At 6 months: diabetes on metformin

BMI: body mass index; * not documented

defined by Dahms to be present when “small groups of beta cells were scattered through acinar tissue, independently from the islets of Langerhans”. Islet hyperplasia was defined as an increase in the number and/or size of islets; and adenomatosis as non-capsulated collection of islet cells large enough to extend through several low power fields.⁵

However, later quantitative immuno-histo-morphometric studies have shown that the features of ducto-insular complexes, islet hypertrophy and islet cell proliferation, characteristic of the normal developing human pancreas, may also be found in normal adults and children, and thus may not be the underlying cause of endogenous hyperinsulinism.⁶⁻⁸ There is evidence from animal studies that pancreatic beta cell mass undergoes remodelling even in the adult stage, from a combination of beta cell replication and apoptosis, and ductal neogenesis.^{9,10} In human studies, cases previously diagnosed as having pathologic nesidioblastosis have been shown to have total endocrine cell mass, islet size distribution and relationship between insulin, somatostatin, and glucagon-secreting cells similar to controls.^{7,8} In contrast, Ariel et al¹¹ reported that the loss of uniformity of beta cells, with the presence of enlarged hyper-chromatic nuclei was a reliable diagnostic criterion distinguishing paediatric hyperinsulinism from normal controls.

The frequent recurrence of hypoglycaemia after 60% to 75% pancreatic resection also suggests that underlying functional defects other than increased beta cell mass may be involved.¹² In infants, such functional defects responsible

for hyperinsulinism have been elucidated at the molecular level and shown to be heterogeneous, involving mutations in the sulphonylurea receptor type 1 (SUR1) gene, the inward-rectifying potassium channel gene, the glucokinase gene and other genes.^{13,14} It is interesting to speculate if similar acquired gene defects could be responsible for the hyperinsulinism associated with adult onset nesidioblastosis and islet hyperplasia.

The above histologic features also occur in several conditions without hyperinsulinaemic hypoglycaemia, such as chronic pancreatitis, obesity,¹⁵ states of insulin resistance,¹⁶ and tolbutamide therapy,¹⁷ all of which may be associated with diabetes. In chronic pancreatitis and insulin resistance, islet hyperplasia and nesidioblastosis could be a secondary phenomenon, reflecting a compensating mechanism for beta cell destruction or functional insufficiency.⁶ Although obesity and insulin resistance may have contributed to our patient's histologic findings, chronic sulphonylurea therapy seems unlikely, because of the short duration of administration. Moreover, sulphonylurea treatment induces an increase in alpha cells and not beta cells,¹⁷ contrary to the intense staining of beta-cells noted in our patient.

Her contrast enhanced CT scan of the pancreas was normal, as expected for a diffuse disease, but it may also be normal in 40% to 60% of insulinomas, since the latter are usually small tumours.^{18,19} However, as portal venous sampling seemed to suggest tumour regionalisation to the pancreatic neck, the postoperative finding of diffuse hyperplasia in our patient was rather unexpected. The

spurious localisation in our patient rested on 3 high values near the junction of the splenic vein with the inferior mesenteric vein (Fig. 1). It may have resulted from catheter position as it has been shown that up to three-fold variations in insulin levels can occur simply by repeated sampling at the same site in large venous trunks, possibly due to lamellar blood flow,²⁰ or the catheter end being placed near a pancreatic vein drainage point.²¹ To overcome this potential for spurious regionalisation when only large venous trunks are sampled, selective pancreatic vein sampling with simultaneous measurement of peripheral vein background insulin concentration has been advocated.²⁰⁻²³

Our case illustrates the management dilemma when faced with the rare patient with impalpable tumour and negative intraoperative ultrasound findings. In paediatric hyperinsulinism from islet hyperplasia, which tends to be resistant to diazoxide therapy, as well as selected adult cases who have severe hyperinsulinism and are unresponsive to or intolerant of high doses of diazoxide therapy, a case for an invasive preoperative regionalising procedure such as porto-pancreatic vein sampling could be made, since it may provide a clue to diffuse disease (although it was falsely localising in our case); or it may give the only localising information of focal disease and allow an informed resection, thus avoiding morbid blind subtotal resections, and even failed distal resections, if focal disease happened to be located in the pancreatic head or uncinate process.^{24,25}

The best surgical approach when faced with the patient with impalpable tumour and negative intraoperative ultrasound in the absence of preoperative localisation data remains controversial. It is impossible to recognise diffuse islet hyperplasia and nesidioblastosis on frozen sections.²⁶ If medical therapy was effective and well tolerated, a conservative approach with repeat localisation at a later date could be advocated. However, if medical therapy was ineffective or poorly tolerated, blind partial pancreatectomy may lead to surgical cure if diffuse islet hyperplasia was the diagnostic entity, as in our case.

In diffuse islet hyperplasia, the extent of pancreatic resection necessary to achieve normoglycaemia is uncertain, even more so for a previously diabetic patient. In non-diabetic patients who respond to diazoxide therapy, a subtotal 75% to 80% pancreatectomy has been recommended, with greater than 90% resection being reserved for a non-responder to medical therapy.^{25,27} Our patient seemed to have severe hyperinsulinism as she developed hypoglycaemic symptoms even without fasting, although she could be controlled on diazoxide therapy. She reverted to a diabetic state well controlled on metformin therapy after 85% pancreatectomy.

Conclusion

In summary, we describe a patient with type 2 diabetes who developed hyperinsulinaemic hypoglycaemia associated with islet hyperplasia. When hypoglycaemia occurs in a diabetic patient after complete withdrawal of hypoglycaemic agents, other causes, including endogenous hyperinsulinism, need to be considered. Insulinoma needs to be excluded because it is the commonest cause of endogenous hyperinsulinism in adults with or without pre-existing diabetes. The entity of islet cell hyperplasia with nesidioblastosis is rare, but it may occur in obese type 2 diabetics and remains a diagnosis of exclusion which can only be confirmed by surgical pathology. Preoperative portal venous sampling may suggest diffuse disease if insulin levels are raised multifocally, but it can be falsely localising, especially if selective sampling of the smaller peri-pancreatic veins is omitted, as illustrated in our case. Definite treatment involves pancreatectomy, although the extent of surgical resection is not well established.

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