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**Adult focal  $\beta$ -cell nesidioblastosis: A case report**

Tu K *et al.* Adult Focal  $\beta$ -cell Nesidioblastosis

Kui Tu, Li-Jin Zhao, Jin Gu

**Abstract****BACKGROUND**

Nesidioblastosis usually refers to a series of clinical manifestations caused by the proliferation of  $\beta$ -cells in pancreatic islets, and these clinical manifestations are hyperinsulinemia and persistent hypoglycemia. According to the size of the lesion, nesidioblastosis is divided into focal nesidioblastosis, diffuse nesidioblastosis and atypical nesidioblastosis, and its pathogenesis is still unclear. Nesidioblastosis is mainly seen in infants and rarely reported in adults, especially focal nesidioblastosis, which is difficult to distinguish from insulinoma.

**CASE SUMMARY**

We report a case of adult focal  $\beta$ -cell nesidioblastosis in which the preoperative diagnosis was insulinoma. The patient was a 48-year-old male who suffered from repeated morning and fasting palpitations, sweating, and severe disturbance of consciousness for 5 years. His blood glucose was found to be as low as 1.79 mmol/L during an attack. However, abdominal computed tomography showed no abnormalities. Magnetic resonance imaging and endoscopic ultrasonography demonstrated a nodular mass in

the head of the pancreas, combined with hyperinsulinemia and high serum C-peptide. The patient was diagnosed with insulinoma and underwent Beger surgery; however, the postoperative pathological results showed nesidioblastosis.

## CONCLUSION

Although surgical resection is the preferred option for nesidioblastosis, some cases can be treated non-surgically. In order to increase clinicians' understanding of nesidioblastosis, it is necessary to review the pathogenesis, diagnosis and treatment of this disease.

**Key Words:** Focal nesidioblastosis; Hyperinsulinemia; Persistent hypoglycemia; Case report

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**Core Tip:** Focal nesidioblastosis is a neuroendocrine disease which is rarely reported in adults and easily confused with insulinoma, and its pathogenesis is still unclear. We report a rare case of adult focal  $\beta$ -cell nesidioblastosis, which was diagnosed as insulinoma before surgery. Increased glucose level after resection of the lesion may assist in the diagnosis of focal  $\beta$ -cell nesidioblastosis, due to intra-pancreatic regulation in focal nesidioblastosis. We also review the related literature. This case report may enhance clinicians' understanding of this disease.

## **1** INTRODUCTION

Nesidioblastosis usually refers to a series of clinical manifestations caused by the proliferation of  $\alpha$  cells or  $\beta$  cells in pancreatic islets. Pathologically, islet structure is normal, but islet cells show hypertrophy, with pleomorphic changes in the nucleus, an increased and transparent cytoplasm, and some pancreatic endocrine cells sprout on pancreatic microducts<sup>[1]</sup>. The clinical

manifestations of  $\beta$ -cell nesidioblastosis are hyperinsulinemia and persistent hypoglycemia. According to the size of the lesion,  $\beta$ -cell nesidioblastosis is divided into focal nesidioblastosis, diffuse nesidioblastosis and atypical nesidioblastosis<sup>[2]</sup>. We report a case of adult focal  $\beta$ -cell nesidioblastosis in which the preoperative diagnosis was insulinoma, and review the possible pathogenesis, imaging manifestations, treatment and progression of  $\beta$ -cell nesidioblastosis.

## **1** CASE PRESENTATION

### *Chief complaints*

A 48-year-old male patient suffered from repeated morning and fasting palpitations, sweating, and severe disturbance of consciousness for 5 years.

### *History of present illness*

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Five years ago, the patient suffered from palpitation and sweating in the morning or after starvation, which were relieved after food eating.

During the 5 years, these symptoms occurred repeatedly, with an increasing frequency year by year. More than 10 attacks and two episodes of comas occurred last year. After glucose injection, his symptoms were alleviated. During the attacks, the patient had no abdominal pain, distension and other discomfort. The patient's weight increased by about 10kg over the past 5 years, and there was no obvious abnormality in urine and stool tests.

### *History of past illness*

There was no specific history.

### **1** *Personal and family history*

All family members were healthy and denied any history of genetic disease and genetic predisposition.

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### **Physical examinations**

Nervous system, cardiopulmonary and abdominal examinations showed no positive signs.

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### **Laboratory examinations**

Blood glucose was measured to be as low as 1.79 mmol/L during an attack, which was relieved after oral food or glucose supplementation. Blood pressure was 160/80 mmHg after admission, and the patient's body mass index was 27.064 kg/m<sup>2</sup>. Blood tests showed that there were no obvious abnormalities in relation to liver function and kidney function. Fasting serum insulin was 219.3  $\mu$ IU/mL (normal value 2.6-24.9  $\mu$ IU/mL), and fasting C-peptide was 6440 pmol/L (normal value 370-1470 pmol/L).

### **Imaging examinations**

Abdominal computed tomography (CT) showed no abnormalities.

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Abdominal magnetic resonance imaging (MRI) revealed a small, slightly long T1 signal nodule in the head of the pancreas, about 10 x 12 mm in size, with a clear boundary and mild enhancement on the enhanced scan, suggesting a tumor (Figure 1). Endoscopic ultrasonography suggested a hypoechoic lesion in the head of the pancreas, with a hyperechoic nodule about 1 x 1.4 cm in size, which was thought to be insulinoma (Figure 2). Positron emission tomography (PET)-CT showed that 68GA-DOTA-TATE was increased in the head of the pancreas, suggesting a possible neuroendocrine tumor.

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### **FINAL DIAGNOSIS**

Based on the above clinical data of the Whipple triad, significantly increased insulin and C-peptide, and imaging suggesting pancreatic head occupation, the patient was considered to have an insulinoma.

## **TREATMENT**

After obtaining consent from the patient and his family, he underwent Beger surgery (duodenum preserving resection of the head of the pancreas).

## **OUTCOME AND FOLLOW-UP**

Two weeks after surgery, the patient did not have hypoglycemia, and serum insulin and C-peptide gradually returned to normal, no significant change in weight. Postoperative changes in blood glucose, insulin and C-peptide are shown in Figure 3; however, the postoperative pathological results suggested nesidioblastosis, and immunohistochemistry showed CK (+), Syn (+), MGMT (+), CD56 (-), CgA (-), Insulin (-), Ki-67 approximately 2% (+), and SSTR2 (0) (Figure 4). Unfortunately, after the patient left the hospital two weeks after surgery, he could not be contacted again.

## **DISCUSSION**

Nesidioblastosis was coined by Laidlaw in 1938, its pathological characteristics are islet hyperplasia, endocrine cell dysplasia, islet cell adenomatosis, and ductoinsular proliferation<sup>[2]</sup>. It is mainly seen in infants with an incidence of between approximately 1 in 25,000 to 50,000, and focal nesidioblastosis accounts for 30–40%<sup>[3]</sup>. It has rarely been reported in adults, especially focal nesidioblastosis, but precise figures do not exist.

In infant nesidioblastosis, mutations in gene ABCC8 coding for the sulfonylurea receptor and gene KCNJ11 coding for inward rectifying K<sup>+</sup> channels are thought to be the main causes of the disease, and these mutations disable the function of the  $\beta$ -cell membrane ATP-sensitive K<sup>+</sup> (K<sub>ATP</sub>) channels which results in channel depolarization and inappropriate insulin secretion<sup>[4]</sup>. The main cause of focal nesidioblastosis is the mutation of paternally inherited ABCC8 and the somatic loss of the maternal 11p allele involving the ABCC8 and KCNJ11 region<sup>[5]</sup>. Through the detection of

proinsulin mRNA and proinsulin in focal nesidioblastosis lesions, it was found that proinsulin mRNA was similar to that in adjacent islets but the level of proinsulin was higher than that in adjacent islets, which indicated that the mutation of these genes effect the level of translation and not transcription<sup>[6]</sup>. Other metabolic disorders can also result in nesidioblastosis, such as glycogen storage disease, by activating mutations of the monocarboxylate transporter-1, and deficiency of glucose transporter-2<sup>[7]</sup>. The pathogenesis of adult nesidioblastosis may be different from infantile nesidioblastosis caused by a genetic effect. Some studies suggest that bariatric surgery, especially Roux-en-Y gastric bypass (RYGB) was one of the reasons for nesidioblastosis. The evidence for this is that patients who underwent RYGB surgery developed hypoglycemia, and to cure hypoglycemia, they then underwent partial pancreatectomy, and the histologic features of the pancreas specimens showed islet hypertrophy and enlarged hyperchromatic pancreatic  $\beta$ -cell nuclei, which are characteristic of nesidioblastosis. The likely mechanism is that the rapid entry of food into the terminal ileum after gastric bypass surgery stimulates excessive release of glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) which then stimulates  $\beta$ -cell release of insulin and reduces alpha-cell release of glucagon<sup>[8]</sup>, producing islet hyperplasia,  $\beta$ -cell pleomorphic nuclei and abundant cytoplasm. Christ *et al* found that the GLP-1 receptor density within the surgical specimen of a patient with focal nesidioblastosis was 3 times the normal density<sup>[9]</sup>. Other possible mechanisms include changes in intestinal absorption of glucose by gut microbiota, decreased secretion of ghrelin, and a reduction of insulin counter-regulatory hormone after gastric bypass surgery<sup>[8]</sup>. The precise mechanism by which RYGB contributes to nesidioblastosis is still not well understood, and further studies are necessary. In focal nesidioblastosis, adjacent islets are small, packed endocrine cells with scanty cytoplasm, which may be the result of intra-pancreatic regulation of



islet  $\beta$ -cells at the translational level<sup>[6]</sup>. This was demonstrated by the patient's elevated blood glucose after surgery.

Nesidioblastosis is a rare disease, the clinical presentation is similar to that of insulinoma, and both cause persistent hypoglycemia and the Whipple triad. Therefore, it is difficult to diagnose nesidioblastosis in adults on the basis of clinical features, and the final diagnosis relies on pathologic analysis of the pancreatic tissue. Conventional imaging has limited sensitivity, especially for diffuse nesidioblastosis in which histological structure is similar to normal pancreatic tissue and lesions spread throughout the pancreas. For focal nesidioblastosis, conventional imaging sensitivity may be similar to the sensitivity to insulinoma: arterial calcium stimulation and venous sampling (ASVS) (85%), endoscopic ultrasonography (EUS) (76%), MRI (58%) and CT (54%)<sup>[10]</sup>. Despite the high positive rate of ASVS, its limited localization and invasiveness has restricted its clinical application. For some types of nesidioblastosis which highly express glucagon-like peptide-1 receptors (GLP-1R), they can be visualized by PET/CT with GLP-1R radiolabeled analogue (68Ga-DOTA-exendin-4) (Exendin). Victor Kalff *et al*<sup>[11]</sup> in a retrospective study found that Exendin correctly identified diffuse nesidioblastosis in 2/3 cases requiring partial pancreatectomy for hypoglycemia control. Some studies have even suggested that the sensitivity of 68 Ga-DOTA-exendin-4 PET/CT was higher than 97%<sup>[7]</sup>, and considerably higher than SPECT/CT (67.5%) and MRI (67.6%)<sup>[10]</sup>. However, there were a number of false-negative readings, and nesidioblastosis needs to be distinguished from peripancreatic uptake and insulinoma. Despite the high accuracy, this method is expensive and injection of Exendin can cause severe hypoglycemia and nausea<sup>[12]</sup>; therefore, the first step in diagnosing the disease is a comprehensive analysis of the clinical history and full biochemical characterization, when 68 Ga-DOTA-exendin-4 PET/CT is positive, endoscopic ultrasound and MRI can be used to confirm the location.



At present, the most effective treatment for adult nesidioblastosis is total or partial surgical resection of the pancreas. Some patients can achieve clinical cure, especially those with focal nesidioblastosis, but partial pancreatectomy is only beneficial in 50% of nesidioblastosis patients and carries a high risk of complications, such as pancreatic fistula, postoperative bleeding, infection, and diabetes. According to the 2016 International Study Group on Pancreatic Surgery data, the dreaded complication of pancreatic fistula still ranges between 3–45% following pancreatic surgery at high volume centers<sup>[13]</sup> and a study reported that 40% of patients developed insulin-dependent diabetes after near-total pancreatectomy<sup>[14]</sup>. It is not possible to predict recurrence of hypoglycemia in adult patients with nesidioblastosis. Medications are also used in the treatment of nesidioblastosis, and the first-line drug is diazoxide. A study researching diazoxide concentrations in maternal and infant blood showed that diazoxide had no harmful effects in infants<sup>[15]</sup>, but its side effects and ineffectiveness in some forms have limited its use in clinical application<sup>[16]</sup>. The second-line drugs are somatostatin analogues, including octreotide and lanreotide. Rina Kato *et al* reported a case of adult-onset nesidioblastosis which was successfully treated with pancreaticoduodenectomy and octreotide<sup>[17]</sup>, but their poor affinity to somatostatin receptors resulting in reduced efficiency. Pasireotide is another somatostatin analogue with a higher affinity to somatostatin receptors, and its long-acting release has been proved effective in isolated nesidioblastosis<sup>[18]</sup>. Other medications include glucocorticoids and calcium channel-blocking agents. Medication to treat nesidioblastosis has varying efficacy and causes side effects. A novel treatment method for nesidioblastosis has been reported, where exendin-4-IRDye700DX, targeting the GLP-1R, was shown to kill  $\beta$ -cells highly selectively; thus, this could in the future provide a new, minimally invasive and highly specific treatment for nesidioblastosis<sup>[19]</sup>. Treatment of nesidioblastosis is not always simple, it is not only dependent on

medication and surgery, but also requires dietary control, dividing food intake into five to six daily meals, slowing gastric emptying, using fructose and avoiding stress at meals. Uncooked cornstarch is a source of slow release carbohydrates, it can produce low glucose peaks and maintains a stable blood glucose level during fasting; therefore, uncooked cornstarch can be considered in patients with persistent hypoglycemia particularly when surgery is impracticable/unaccepted and pharmacologic therapy is ineffective<sup>[20]</sup>.

## **1** **CONCLUSION**

The preoperative differentiation of adult nesidioblastosis from an insulinoma is very difficult. The pathogenesis of nesidioblastosis requires further study and it can be cured by partial or subtotal pancreatectomy. However, in some cases, a combination of medication and dietary control may be useful and surgery can be avoided. It can be concluded from the present case, that focal nesidioblastosis can also occur in adults, although it is extremely rare. The diagnosis of hyperinsulinemia and persistent hypoglycemia in patients with an isolated lesion in the pancreas should not be limited to insulinoma. Increased glucose level beyond the normal range after resection of the lesion may assist in the diagnosis of focal  $\beta$ -cell nesidioblastosis, due to intra-pancreatic regulation in focal nesidioblastosis.

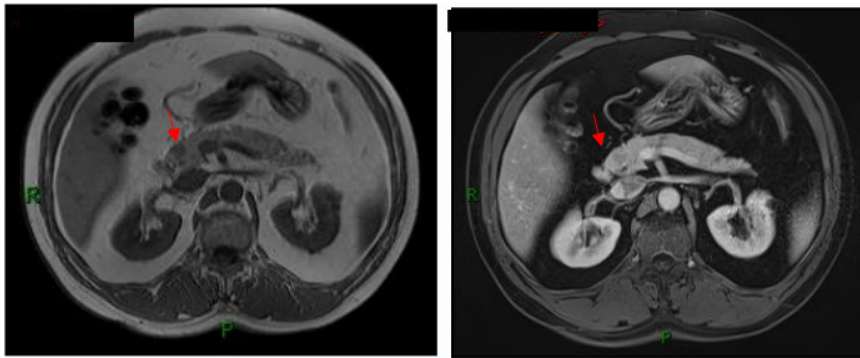
## **2** **Footnotes**

Informed consent statement: Informed written consent was obtained from the patient for publication of this report and any accompanying images.

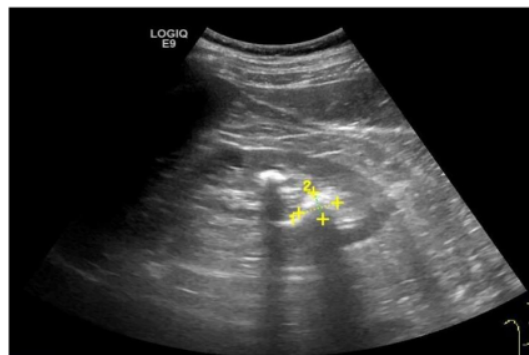
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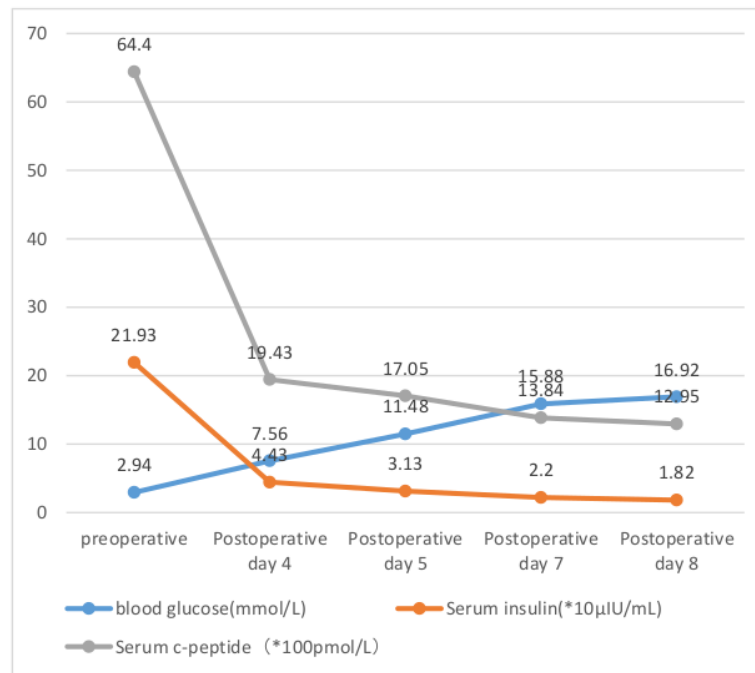
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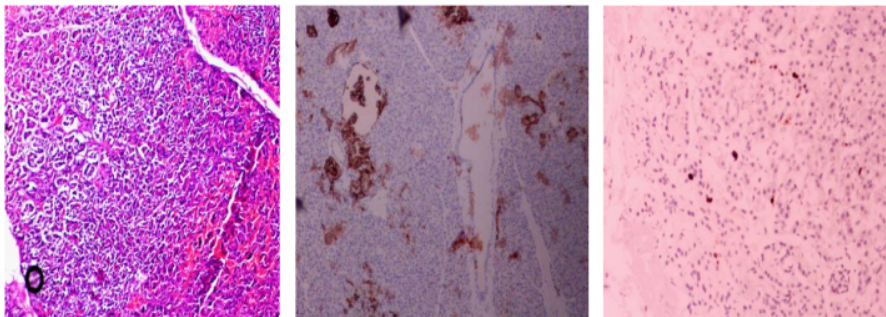
**Figure 1** Small and slightly long T1 signal nodules were seen in the head of the pancreas with clear boundaries and mild enhancement.



**Figure 2** Endoscopic ultrasonography suggested a hypoechoic lesion in the head of the pancreas, with a hyperechoic nodule, about 1 cm x 1.4 cm in size.



**Figure 3** Preoperative and postoperative changes of **fasting** blood glucose, insulin and C-peptide.



**Figure 4** Postoperative pathological results showed nesidioblastosis:islet cells show hypertrophy, with pleomorphic changes in the nucleus, an increased and transparent cytoplasm(Left), and immunohistochemistry

analysis showed Ki-67 about 2% (+)(Middle), Syn (+)(Right), MGMT (+), CD56 (-), CgA (-), Insulin (-), CK(+).

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