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Case Report

Adult Nesidioblastosis With Hypoglycemia Mimicking an Insulinoma: A Challenging Case

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Introduction: Nesidioblastosis is the primary cause of persistent hyperinsulinemic hypoglycemia in infants but it is a rare entity for the adults. Nesidioblastosis is defined as an increase of pancreatic beta cells in number and in size. Case Presentation: We describe a rare case of nesidioblastosis with positive endoscopic ultrasonography result mimicking an insulinoma. A 35-year-old female patient had hypoglycemic episodes with high insulin level. Her investigation revealed low venous plasma glucose, high insulin and C-peptide level with positive 72-hour fasting test suggestive of hyperinsulinemic hypoglycemia. Abdominal computed tomography did not show any mass lesion. Endoscopic ultrasonography revealed a mass lesion sized as 1 cm in diameter in the pancreas. But, insulinoma like lesion couldn't be found intra-operatively. It was decided to perform distal pancreatectomy. After distal pancreatectomy, nesidioblastosis was diagnosed histopathologically. The patient was free from her symptoms after surgery. Conclusion: This case illustrates difficulties and limitations of imaging modalities and false positive result of EUS in a case of nesidioblastosis. When there is no insulinoma like lesion during operation, operation should be performed as gradient guided pancreatectomy by the way of selective arterial calcium injection test.

Key words: nesidioblastosis, endoscopic ultrasonography, insulinoma

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Nesidioblastosis is the primary cause of persistent hyperinsulinemic hypoglycemia in infants but it is a rare entity for the adults. Nesidioblastosis is defined as an increase of pancreatic beta cells in number and in size. There is focal or diffuse hypertrophy and hyperfunction.[1] It was indicated as noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) in terminological terms by Service in 1999.[2] Nesidioblastosis is the histopathological equivalent of NIPHS. The neoformation of islets of Langerhans from the pancreatic ductal epithelium was seen in nesidioblastosis. In adults, hyperinsulinemic hypoglycemia is caused mostly by insulinoma. Nesidioblastosis was seen as 0.5%–5% cases of adult hyperinsulinemic hypoglycemia cases.[3] Based on clinical and radiological features, it is often difficult to distinguish NIPHS from insulinoma.

We describe a rare case of nesidioblastosis with false positive endoscopic ultrasonography finding mimicking an insulinoma. Treatment modalities for nesidioblastosis are discussed based on the current literature.

Case Report

A 35-year-old Caucasian female patient was admitted to our department with complaints of tingling of the lips, tremor and nervousness. She had episodes of fasting hypoglycemia. There was a history of diabetes in her aunt. She declared that she was not taking any medication related to diabetes. Unfortunately, we couldn't perform sulfonylurea screen test in plasma. The 72-hour fasting test showed hyperinsulinemic hypoglycemia which was detected at 15. hour with the fasting plasma glucose, insulin and C-peptide levels as 45 mg/dL, 9.9 mIU/mL and 1.84 ng/mL, respectively. Based on laboratory findings, there was no hypocortisolism and the patient was euthyroid. Dynamic computed tomography (CT) scanning did not reveal any mass lesion in the pancreas. Endoscopic ultrasonography (EUS) pointed a lesion in the body of pancreas close to splenic vein consistent with insulinoma measured as 1 cm in diameter. The patient underwent an operation with the possible diagnosis of insulinoma. However, adenomatous lesion in pancreas couldn't be palpated intraoperatively. Thus, distal pancreatectomy was performed with laparoscopic technique. Histopathological study of the resected pancreatic tissue revealed that there was increment in number of islet cells and in size as well. It was observed that islet cells were budding from the pancreatic duct epithelium forming "ductuloinsular complex." Immunohistochemical analysis showed positive staining with chromogranin A, synaptophysin and cytokeratin 7 (see Fig 1). Based on histopathological and immunohistochemical findings, it was diagnosed as nesidioblastosis. After the surgery, the patient was free from her symptoms. There was no hypo or hyperglycemia during follow-up period.

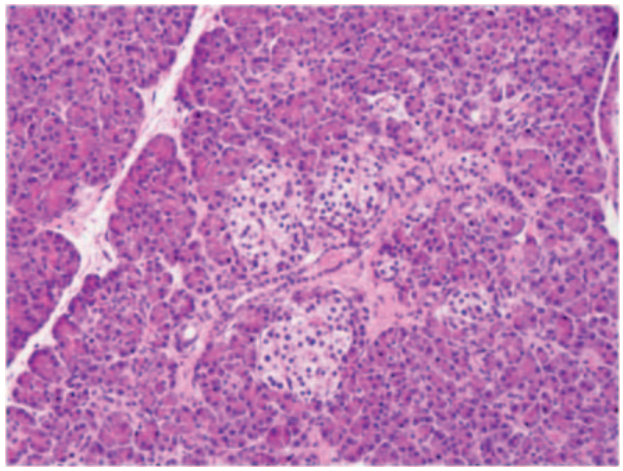

Fig. 1 Histologic section of pancreas. Chromogranin immunostain demonastrating endocrine cells within irregular islets (chromogranin, 10x).

Conclusion

Based on clinical and laboratory findings, hyperinsulinemic hypoglycemia was diagnosed in our patient. Insulinoma like mass lesion in pancreas was reported in EUS. Intraoperatively insulinoma was not palpated and distal pancreatectomy was performed. After surgery nesidioblastosis was diagnosed histopathologically.

Diagnosis of nesidioblastosis in preoperative period is a challenge for the clinicians, because it does not differ so much from insulinoma clinically. There are no clear-cut criteria for differentiation of nesidioblastosis from insulinoma. Generally, it is diagnosed after surgery histopathologically. Insulinomas have usually uniform nuclei and small nucleoli. In nesidioblastosis multiple beta cells have enlarged and hyperchromatic nucleus and abundant clear cytoplasm.[4] Nesidioblastosis is characterized by budding of islet cells from the duct epithelium increased in size, shape and number. In nesidioblastosis, islet cells form "ductuluoinsular complex". In our patient, this complex was observed in pancreatic resection material as shown in Figure

1. Other histologic criteria for nesidioblastosis include microscopic, macroscopic and immunohistochemical exclusion of insulinoma. Endocrine cells should not show any proliferative activity of the ki-67 antigen.[4]

After hyperinsulinemic hypoglycemia was defined, in order to detect insulinoma mass lesion, imaging modalities like CT, MRI, EUS, somatostatin receptor scintigraphy are performed. If the mass lesion is not found by those techniques, possibility of nesidioblastosis comes out. Even so, occult insulinoma cannot be ruled out. In this case selective arterial calcium injection test becomes more of an issue.[5] This method shows hyperfunction and also points to localization so that gradient-guided resection can be performed. In our case, because of the positive EUS finding, we thought that hyperinsulinemic hypoglycemia was due to the insulinoma. So, we didn't perform selective arterial calcium injection test. Although EUS is a remarkably reliable procedure for the preoperative localization, it may give both false-positive and false-negative results. EUS is an imaging modality for insulinoma with a sensitivity rate of 86.6%–92.3%.[6] 68Ga-DOTA-exendin-4 PET/CT (Positron Emission Tomography/Computed Tomography) may be used to detect nesidioblastosis.[7] It was shown that more than 3-times higher density of GLP-1R (glucagon like peptide-1 receptor) were present in nesidioblastosis when compared with normal pancreas.[8] One patient reported by Christ et al.[7] was diagnosed with nesidioblastosis histologically. 68Ga-DOTA-exendin-4 PET/CT was performed preoperatively and an increased uptake from the tail of the pancreas to the pancreatic corpus was demonstrated. According to that result, left sided pancreatectomy was performed. This noninvasive tool provided the detection of nesidioblastosis and correct surgical decision. Raffel et al.[4] suggests that if there is one positive test for localization, local resection should be performed. If there is negative preoperative localization result, then selective arterial calcium injection test should be performed. The main problem regarding to imaging techniques is the fact that they are not sensitive enough to distinguish focal from diffuse organic hyperinsulinemia. Insulinoma lesions are generally as small as 3 to 10 mm and may not be seen in those imaging modalities.[4] Besides, false positivity is another issue. Therefore, selective arterial calcium injection test allows focal hyperactive beta cells disease to be distinguished from diffuse disease. It was shown that selective arterial calcium injection test was useful in differentiating insulinoma from nesidioblastosis with high specifity in case of negative imaging results.[9] Gradient-guided pancreatectomy can be possible with selective arterial calcium injection test. On the other hand, with unnecessary "too much" operation, endocrine/exocrine pancreas insufficiency may occur. Retrospectively, we thought that we should have performed SACI test in our patient although the extent of surgery was successful at the moment. During follow-up period there were no hypo or hyperglycemia. Surgery shouldn't be performed without preoperative localization ideally. If insulinoma lesion can't be localized during surgery, it is recommended surgery should be stopped to avoid blind distal pancreatectomy.[10] Kimmerly et al. [11] reported that all patients with nesidioblastosis who had pancreatic resection got rid of their hypoglycemic symptoms but nearly 90% of them had recurrences of hypoglycemia in their follow-up period. Although Witteles et al.[12] indicated that 70% distal pancreatectomy for nesidioblastosis was successful as regards to resolution of hypoglycemia, 2 out of 5 patients with blind distal pancreatectomy had recurrences of hypoglycemia.

Thompson[13] recorded that SACI test was performed for their 10 cases of hyperinsulinemic hypoglycemia with negative radiologic imaging of pancreas. In 6 cases, an extended distal pancreatectomy was performed to the right of the superior mesenteric vein. In 4 cases, gradient was confined to splenic artery in selective arterial calcium injection test; resection was performed to the left of the superior mesenteric vein. All the patients had relief of their symptoms.[13]

In Won's study, clinical features of 10 nesidioblastosis patients were examined. In this study, 6 of 10 patients were performed gradient-guided subtotal (70%) or distal (50%) pancreatectomy. In 3 of operated 6 patients, 70% subtotal (splenic and superior mesenteric arteries) pancreatectomy was carried out. One of these patients had developed diabetes. 50% distal pancreatectomy was performed in other 3 patients. The other 4 of 10 patients were given medical therapy as diazoxide.[6] Diazoxide can be an option in treatment of nesidioblastosis when the patient couldn't tolerate surgery or when the surgery fails.

In conclusion, nesidioblastosis is very rare in adults. This case illustrates difficulties and limitations of imaging modalities and false positive result of EUS in a case of nesidioblastosis mimicking insulinoma. When there is no insulinoma like lesion during operation, blind pancreatectomy should be

abandoned and gradient guided pancreatectomy should be selected by the way of SACI test.

Ethical approval was not required for this case report. The patient had given informed consent.

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