Adulthood Nesidioblastosis: A Case Report

Bir Erişkin Nesidioblastosis Vaka Sunumu

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Abstract

Only a small number of adult patients with persistant hyperinsulinemic hypogycemia (PHH) without insulinoma were reported in the recent years. We want to discuss a 73-year-old man with PHH who was brought in to the emergency service with a low blood glucose level. Subtotal pancreatectomy was performed under general anesthesia without a tumoral mass. The histopathological examination revealed ductuloinsular complexes. One giant islet measuring 800µm x 300µm was observed. The mean islet diameter was 270 µm, and 24 % of the islets were over 300 µm in size. The mean beta cell nucleus diameter was 7.27µm (5.28µm in the control group). Postoperatively, patient's blood glucose measurements remained within normal limits.

In conclusion; ductuloinsular complex formation, islet cell hyperplasia and Ki-67 immunolabeling are not valuable diagnostic criteria for the diagnosis of adulthood nesidioblastosis. The most valuable histopathological feature is beta cell nucleus size. *Turk Jem 2007; 11: 67-9*

Key words: Adulthood nesidioblastosis, morphometric analysis, Ki-67, hyperinsulinemic hypoglycemia

Özet

Son yıllarda dirençli hiperinsülinemik hipoglisemi gelişen ancak insülinoma tespit edilemiyen çok az sayıda erişkin vaka bildirilmiştir. Acil servise düşük kan şekeri düzeyleri ile getirilen, 73 yaşında erkek bir hastayı tartışmak istiyoruz. Genel anastezi altında uygulanan subtotal pankreatektomi esnasında tümöral dokuya rastlanılmadı. Histopatolojik incelemede duktuloinsülar kompleksler gözlemlendi. Bir adet 800µm x 300µm boyutlarında dev adacık gözlendi. Ortalama adacık büyüklüğü 270 µm saptandı ve adacıkların % 24'ünün büyüklüğü 300 µm üzerindeydi. Ortalama beta hücre nükleus boyutu 7.27 µm olarak saptandı (kontrol grubunda 5.28 µm). Operasyon sonrası dönemde hastanın kan glukoz düzeyleri normal limitler içinde seyretti. Sonuç olarak; duktuloinsülar kompleks oluşumu, adacık hicre hiperplazisi veya Ki-67 ile immün işaretleme erişkin nesidioblastosis tanısında değerli birer tanı kriteri değildir. En değerli histopatolojik bulgu beta hücre nükleus boyutudur. *Turk Jem 2007; 11: 67-9*

Anahtar kelimeler: Erişkin nesidioblastosis, morfometrik analiz, Ki-67, hiperinsülinemik hipoglisemi

Introduction

Persistent hyperinsulinemic hypoglycemia (PHH) is caused by impaired control of insulin release from functionally defective pancreatic ß cells. Insulinomas are the most common cause of PHH in adults. In the newborns with PHH, the functional defect of the ß cell resides in the glucose-sensor system and this defect is due to inactivating mutations of KATP. In the recent years, more adult patients with PHH were reported in whom no insulinoma could be detected. These patients with PHH improved after partial resection of the pancreas. Histopathologic examination of the islets showed similar changes to those reported in newborns (1,2,3).

The term nesidioblastosis was first introduced by Laidlaw in 1938 to define the proliferation of pancreatic islet cells budding off from ductal epithelium and later it was accepted as a histopathologically heterogenous entity (4,5). Today nesidioblastosis designates morphologic changes in the endocrine pancreas causing PHH in the absence of insulinoma. In 1975, the first adult patient with nesidioblastosis was reported. Since then only a small number of patients have been published (1, 2, 5-12). In this case report, we describe an adult with PHH and without an insulinoma, and discuss the histopathological features of adulthood nesidioblastosis.

Case Report

A 73-year-old man was brought in to the emergency service of Kocaeli University Medical School with the complaint of loss of consciousness. Several fingerstick glucose measurements were between 10 and 29 mg/dl. The patient was admitted by endocrinology department. His plasma glucose concentration was 17 mg/dL while simultaneous plasma insulin concentration was 70.3 µU/mL.

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Radiological examinations including abdominal MR did not reveale any tumoral mass in the pancreas. The patient was transferred to general surgery with the possible diagnosis of insulinoma. After obtaining informed consent, subtotal pancreatectomy was performed without any complication.

The size of the specimen was 12 x 4 x 1.5 cm. The specimen was embedded in 24 blocks. Three sets of serial sections were made from each of the 24 blocks. No tumoral mass was detected. Selected blocks were stained immunohistochemically for chromogranin, insulin, glucagon and somatostatin.

Three specimens from Whipple resections with normal pancreas tissue were served as a control group for morphometric analysis and Ki-67 immunoreactivity. In order to compare the proliferative activity, one paraffin block from our case and three blocks from the control cases got immunostaining for Ki-67. Intranuclear immunoreactivity in 100 islets were measured. The diameter of 100 Langerhans islet cells and the nucleus diameters of 100 beta cells were measured with an ocular micrometer.

The histopathological examination of our case specimen revealed that the lobular architecture of the pancreas was preserved. The endocrine component was composed of abnormally shaped lobulated islets. there were single endocrine cells (Figure 1). One giant islet measuring 800 µm x 300 µm was seen in the 7th serial section of the paraffin block of our case specimen with Ki-67 immunostaining and disappeared in the serial sections (Figure 2). Islets budding of the pancreatic duct and ductuloinsular complexes containing ductular, insular and mixed components were detected. (Figure 3). Insulin immunostaining was seen in more than 80% of the islets and in small clusters and single cells in the paranchyma (Figure 4). The typical peripheric alpha cell ring was not observed in some islets immunostained for glucagon (Figure 5). Ki-67 immunoreactivity was more prominent in the exocrine component than in the endocrine component. Twenty cell nucleus of 100 islets revealed immunoreactivity in our case (mean of 18.1 cell nuclei in the control group). The giant islet was excluded from the morphometric analysis. The mean islet diameter was 270 ± 210 µm, and

24 % of the islets were over 300 µm in size. The mean beta cell nucleus diameter of our case was 7.27 ± 5.62µm (range 2.5 – 13.75µm). The mean diameter in the control group was 5.28 ± 3.8µm (range 2.5 - 10µm). The Ki-67 immunoreactivity, and morphometric analysis of our case and the mean of the three control groups were shown in Table 1.

After the surgery the patient's general condition deteriorated. Patient was transferred to the intensive care unit. The blood glucose levels flactuated between 90–110 mg/dl. The patient died secondary to respiratory failure in the postoperative 48th day. The patient was diagnosed as having adult nesidioblastosis on the basis of clinical and histopathological features.

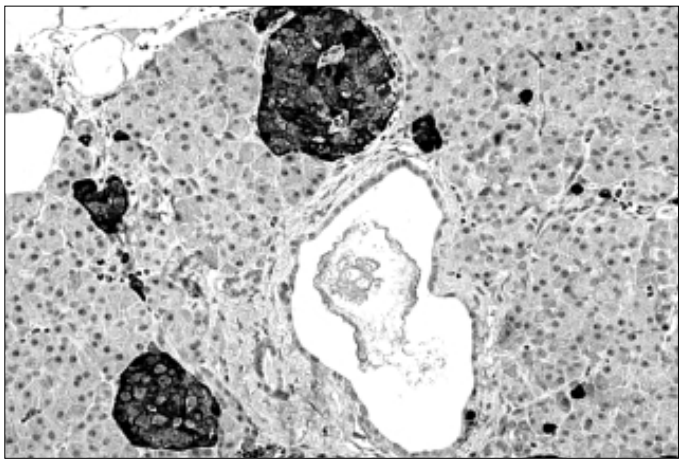

Figure 1. Abnormal shaped Langerhans islets those are located in the periphery of the lobules, near a dilated duct and separated endocrine cells in the pancreas (Immunohistochemistry chromograninX100)

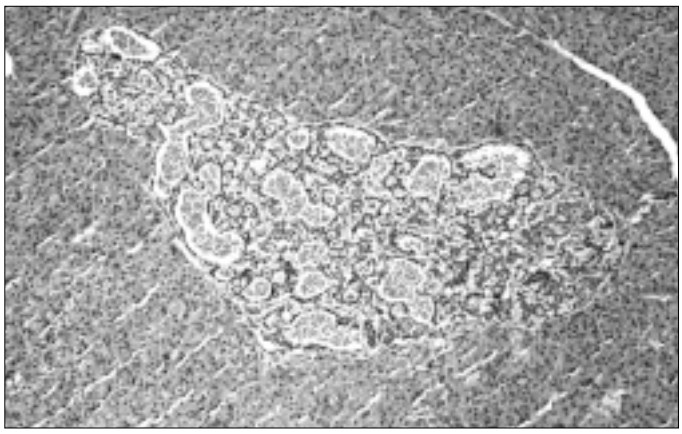

Figure 2. Giant endocrine islet or micro adenoma in the pancreas (HEX40)

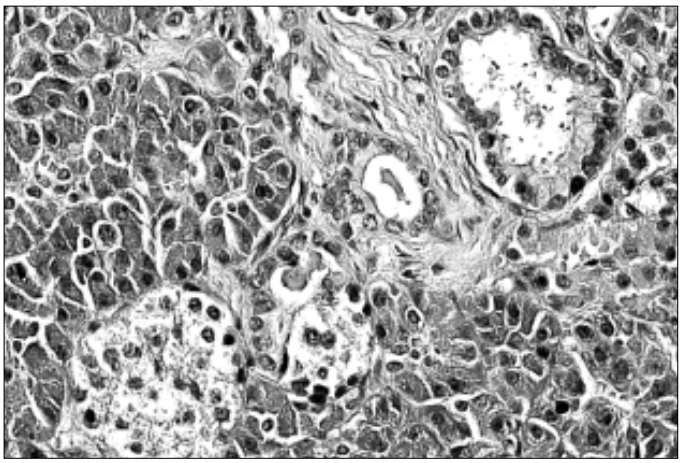

Figure 3. Ductuloinsular complex that consist of a duct on the right, a endocrine islet on the left and a hybrid structure in the middle (HEX200)

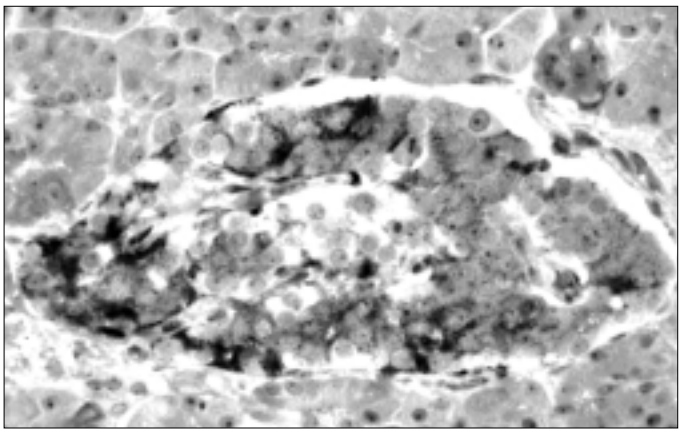

Figure 4. Insulin immunoreactivity in a Langerhans islet (Immunohistochemistry insulin X400)

Discussion

Adult nesidioblastosis is a very rare entity. The typical mutations of newborn nesidioblastosis are in the Kir6.2 and SUR1 genes. Neither of these genes were not detected in adult nesidioblastosis cases (10). 86 cases with the clinical features of hyperinsulinemic hypoglycemia without a tumoral mass were reported until now. All these patients recovered dramatically after the resection procedure (3, 13). The diagnosis of nesidioblastosis requires PHH without an insulinoma. None of the histopathologic criteria like ductuloinsular complexes, islet cell hyperplasia, islets in abnormal shapes, single endocrine cell in the pancreas parenchyma is pathognomonic. These histopathologic features can be observed in the normal pancreas or peritumoral region (14,15, 16, and 17). Islet cell atypia is a criterion for the diagnosis of infant nesidioblastosis but this may not be observed in adulthood nesidioblastosis (16, 18). The beta cell nucleus diameters are significantly different between our case and the control pancreatic specimens (7.27µm vs. 5.28µm). Similar results were reported (6.5±0.99µm vs. 4.99±0.82µm) and beta cell hypertrophy was reported as the most valuable diagnostic criterion (3).

The standard mean Langerhans islet diameter in normal subjects is reported as 200 µm. A diameter more than 500 µm is considered abnormal (14, 19). We found one giant Langerhans islet of 800 µm and another one with more than 500 µm. The Langerhans islet diameter of our case was 270 µm. Values ranging from 220 µm to 620 µm have been reported for adulthood nesidioblastosis cases (3, 14, and 16). In one study, the islet diameter was found to be larger than the control group in 2/3 of the cases (3). The PHH cases in adulthood are not homogeneous for islet diameter measurements. The proliferative activity in the endocrine component of adulthood nesidioblastosis cases was studied by Anlauf et al. The Ki-67 labeling index in 20% of the patients was the same as in the control group (3). In our case, the Ki-67 immunoreactivity is not different from the control group.

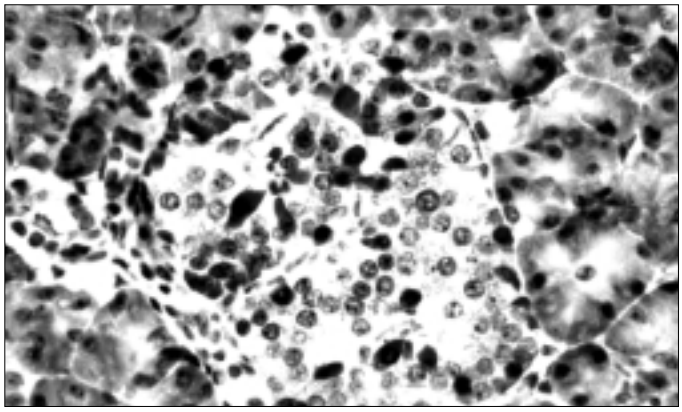

Figure 5. Glucagon immunoreactivity in a Langerhans islet without a typical peripheral ring (Immunohistochemistry glucagon X400)

The histopathological diagnosis of the adult nesidioblastosis is challenging. We also think that beta cell hypertrophy is the most valuable criterion for the diagnosis. The significant difference in the proliferative activity of the endocrine component and the islet diameter may be valuable for some but not for all cases. It is worth remembering that giant islets larger than 900 µm in diameter may be observed in adulthood nesidioblastosis .

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Table 1. The Ki-67 immunoreactivity, Langhans islet diameter and nuclear diameter of beta cells at our case and mean of three control cases

	Ki-67 immunoreactivity in 100 islet (range)	Langhans islet diameter (range)	Nuclear diameter of beta cells (range)
Our case	20	270 ± 210 (70-490) µm	7.27 ± 5.62 (13.75-2.5) µm
Control group (mean)	18	194 ± 165 (70-400) µm	5.28 ± 3.8 (10-2.5)µm