CASE REPORTS

HYPOPITUITARISM AND NESIDIOBLASTOSIS IN AN ELDERLY PATIENT WITH ORBITAL LYMPHOMA

Jin-Ying Lu, Tien-Shang Huang, and Mu-Zon Wu

Abstract: Nesidioblastosis is a rare cause of hyperinsulinemic hypoglycemia in adults. We report a case of combined hypopituitarism with secondary adrenal insufficiency and nesidioblastosis with symptomatic hypoglycemia. This 84-year-old woman had a diagnosis of right side orbital lymphoma and underwent one complete course of local radiotherapy 6 months prior to this admission. Intermittent consciousness alteration had occurred in the 2 months after radiotherapy, and hypoglycemia with a blood glucose of 0.61 mmol/L (11 mg/dL) was noted. Although this case exhibited inappropriate hyperinsulinemia during the hypoglycemic episode, the prolonged fasting test was negative, which was unusual for insulinoma but common to nesidioblastosis. The hypopituitarism and secondary adrenal insufficiency, which may have been radiotherapy related, and the nesidioblastosis led to a relapse of neuroglycopenia. After a glucocorticoid supplement and an 80% subtotal pancreatectomy, her hypoglycemic symptoms were relieved. This case reminds us that nesidioblastosis, in addition to insulinoma, should be considered as a cause of hypoglycemia in elderly patients.

George Laidlow first described nesidioblastosis, a diffuse proliferation of islet cells arising from the pancreatic duct epithelium, in 1938 [1]. Hypoglycemia usually develops in the neonatal period, although adult cases have been reported since 1981 [2]. We report a case of combined hypopituitarism with secondary adrenal insufficiency and nesidioblastosis.

Case Report

This 84-year-old woman presented with intermittent consciousness alteration for about 2 months after receiving radiotherapy for a right side orbital lymphoma. Previously, she was treated for cerebrovascular accident (CVA) and coronary artery disease (CAD) with percutaneous transluminal catheter angioplasty, and had undergone local radiotherapy for cervical cancer in situ. Progressive proptosis of the right eye and deterioration of visual acuity for 2 months led to a diagnosis of orbital small lymphocytic lymphoma in March 1999. There was no evidence of extraocular involvement at the time of diagnosis. Local radiotherapy 4000 cGy in 20 fractions (5 fractions per week for 4 weeks) and systemic chemotherapy with oral chlorambucil 12 mg per day and prednisolone 30 mg per day were administered for a total of 5 days in May 1999.

She was doing well until November 23, 1999, when she developed a change in consciousness with severe diaphoresis in the afternoon. Her husband recalled that she had a poor appetite that noon and only ate some papaya for lunch. She was taken to the emergency room. She was 153 cm in height and 53.7 kg in weight. Her blood pressure was 124/70 mmHg, pulse rate 90/minute, and temperature 37.6°C. The conjunctivas were not anemic and scleras were not icteric. The pupils were isocoric with a prompt light reflex. Her neck was supple, with no goiter, lymph nodes, or jugular vein engorgement. The breathing sound was clear, and heartbeat...
Hypopituitarism and Nesidioblastosis

was regular with only a faint functional murmur. The abdomen was soft and without any tenderness or rebound pain. The liver and spleen were impalpable. The four extremities moved freely, and no pitting edema, cyanosis, or skin lesions were detected.

The plasma glucose was only 0.61 mmol/L (11 mg/dL). After intravenous glucose was given, she regained consciousness. The C-peptide concentration was greater than 14 nmol/L, blood glucose was 5.72 mmol/L (103 mg/dL), and cortisol was 97.95 nmol/L (3.55 µg/dL). Insulinoma had been suspected because of hyperinsulinemic hypoglycemia in a relatively fasting state. Abdominal ultrasonography revealed a pancreatic body tumor and a dilated main pancreatic duct (Fig. 1), although abdominal computerized tomography (CT) scan failed to detect the tumor. Prolonged 72-hour fasting test did not show hypoglycemia (Table). Under the suspicion of misuse of oral hypoglycemic agents (her husband has diabetes mellitus), factitious hypoglycemia was deduced. However, she had another two episodes of fainting and falling down on December 6 and 8, 1999, respectively. Secondary adrenal insufficiency was diagnosed according to the baseline cortisol concentration and the results of a rapid cosyntropin stimulation test. The baseline cortisol and adrenocorticotropin (ACTH) concentrations were 31.54 nmol/L (8 AM) and 97.12 nmol/L (4 PM), and 1.70 pmol/L (8 AM) 2.58 pmol/L (4 PM), respectively. After 1 mg cosyntropin intramuscular injection, the cortisol concentration was 99.32 nmol/L (3.6 µg/dL) at 1 hour. Pituitary magnetic resonance imaging (MRI) revealed a partial empty sella (Fig. 2). Other anterior pituitary hormones were measured, with the following results: growth hormone 0.26 µg/L, free thyroxine 18.66 pmol/L (1.45 ng/dL), hs thyroid stimulating hormone 0.934 mIU/L, luteinizing hormone less than 0.7 IU/L, follicle stimulating hormone 1.2 IU/L, estradiol less than 73.42 pmol/L (20 pg/mL), and progesterone less than 0.64 nmol/L (0.2 ng/mL). Under the diagnosis of hypopituitarism with secondary adrenal insufficiency due to partial empty sella, prednisolone 7.5 mg per day was prescribed.

Another episode of cloudy consciousness and delirium occurred again on January 1, 2000, and she was taken to our emergency room. Blood glucose was less than 0.56 mmol/L (10 mg/dL) on arrival. This episode of hypoglycemia seemed more refractory to glucose administration. Under continuous infusion of glucose water at a rate of about 25 g/hour, the blood glucose was maintained at around 7.22 mmol/L (130 mg/dL). Even a slight tapering of the glucose infusion was followed by a profound change in consciousness and in hypoglycemia.

After admission to a general ward, an intravenous 50% dextrose water infusion was continued via a central venous line and the blood glucose was maintained at 5.33 to 10.55 mmol/L (96–190 mg/dL). Whole body gallium scan, used for detecting lymphoma, showed a suspicious area of mildly increased tracer uptake in the mid-to-upper abdomen. One episode of hypoglycemia (blood glucose 2.44 mmol/L or 44 mg/dL) occurred during admission, manifested by impaired orientation, attention, and language. The concentration of insulin was 365.2 pmol/L and of C-peptide was more than 14 mmol/L. Endoscopic ultrasonography was performed due to suspicion of insulinoma and revealed two anechoic lesions about 1 cm in size in the pancreatic body. Selective angiography of the celiac trunk and gastroduodenal artery via the transfemoral route showed a hypervascular stain located in the pancreatic body supplied by the transverse pancreatic artery. CT angiography showed the same hypervascular nodule in the ventral portion of the pancreatic body. Insulinoma was then highly suspected. After a pneumococcal vaccination, she underwent an uneventful partial, distal pancreatectomy and splenectomy on January 19, 2000. However, intraoperative ultrasonography could not detect any nodule or mass in the pancreas. About 80% pancreatectomy was performed. Chronic inflammatory changes over the pancreas and its capsule with diffuse hard consistency over the pancreatic body were noted. The patient tolerated the whole procedure well. Pathology showed no evidence of insulinoma except for focal fatty change and ischemic necrosis in the body of the pancreas. However, nesidioblastosis, characterized by nests

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**Table.** Prolonged 72-hour fasting test

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>Glucose (mmol/L)</th>
<th>Insulin (pmol/L)</th>
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<tr>
<td>12</td>
<td>3.44</td>
<td>17.22</td>
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<tr>
<td>18</td>
<td>3.44</td>
<td>17.22</td>
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<td>24</td>
<td>3.61</td>
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<td>30</td>
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<tr>
<td>72</td>
<td>3.33</td>
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of endocrine islet cells scattered around the large pancreatic ducts with involvement of section margins, was noted (Fig. 3). The postoperative convalescence was uneventful, and the patient was free of hypoglycemic symptoms during 13 months of outpatient follow-up.

Discussion

Nesidioblastosis, a rarely described disease in adults, has been reported more frequently in the past 10 years. It has been assumed that this disease was underdiagnosed in the past. There have been about 28 reported cases of nesidioblastosis in adults [2–5]. Occasionally, nesidioblastosis has been reported in association with other conditions, including insulinomas, multiple pancreatic islet cell adenomas, multiple endocrine neoplasia type 1, gastrinoma, sulfonylurea therapy, chronic pancreatitis, and cystic fibrosis [3]. However, it has not been previously associated with secondary adrenal insufficiency as in our patient. Hypopituitarism with secondary adrenal insufficiency and nesidioblastosis may both have contributed to the severe neuroglycopenia in our patient.

Hypopituitarism with secondary adrenal insufficiency, which resulted from partial empty sella in our patient, has many other possible underlying causes including idiopathic, lymphocytic hypophysitis, hypovolemic infarction during postpartum hemorrhage, local radiotherapy, and/or surgical resection of previously existing suprasellar tumors [5]. Although radiotherapy for right side orbital lymphoma may have caused the secondary adrenal insufficiency in our patient, the short interval after radiotherapy prior to the development of symptoms and the relatively low radiation dose do not favor this origin. In addition to impairment of the pituitary‐adrenal axis, the gonadotropin level in our patient was abnormally low for her age. Corticotropin and cortisol concentrations were both low, but an insulin hypoglycemic test was not feasible for this patient due to a history of CAD and CVA. A rapid cosyntropin test showed delayed and inadequate cortisol responses. At least two axes of anterior pituitary hormone were impaired in this patient. Constine et al reviewed hypopituitarism in patients who received radiation therapy for nasopharyngeal, extracranial, or primary brain tumors even though the tumors were anatomically distinct from the
hypothalamic-pituitary region [6]. They found that the greater the dose of radiation, the more likely the patient was to develop panhypopituitarism and that the deficiencies in these patients occurred at an earlier time [6]. It has also been reported that the incidence of hypothalamic-pituitary damage was more than 90% at 10 years among patients who underwent external irradiation at doses ranging from 3,750 to 4,250 cGy [7, 8]. Furthermore, cytotoxic agents, such as chlorambucil (an oral alkylating agent) used by our patient, can potentiate the effects of cranial irradiation on hypothalamic-pituitary function and, thus, increase the risk of radiation-induced hypopituitarism [9]. Isolated secondary adrenal insufficiency has been reported to be the sole cause of hypoglycemic syncope in elderly women [10]. Therefore, this diagnosis was made during our patient’s first admission, because her 72-hour fasting test failed to demonstrate hyperinsulinemic hypoglycemia.

Despite glucocorticoid supplementation, our patient still experienced further neurolglycopenic episodes with increasing intensity and frequency 1 month later. Because an elevation of insulin and C-peptide concentrations had been noted without definite exposure to oral hypoglycemic agents, imaging studies were performed to localize the suspected pancreatic insulinoma. The hypoglycemia was episodic in our patient, with no need for continuous glucose infusion during the 2 weeks after admission. Episodic secretion of insulin in nesidioblastosis has been previously described [11, 12]. In addition, unlike the sensitivity seen in about 95% of insulinoma cases, 72-hour fasting test may fail to demonstrate hypoglycemic symptoms in patients with nesidioblastosis [2, 11, 12]. Although angiography, endoscopic ultrasound, and CT angiography showed a vascular blush of about 1 cm in diameter in the pancreatic body, CT scan failed to detect the same lesion. The need for preoperative localization of insulinoma remains controversial. Some authors consider that preoperative localization of insulinoma is not necessary [13]. In cases where the surgeon cannot palpate the insulinoma during the operation due to its small size or, rarely, due to nesidioblastosis as in our patient, it has been proposed that subtotal distal pancreatectomy of about 80% in extent should be performed without enucleating the insulinoma [2, 11–13]. Our patient’s clinical condition dramatically improved after the pancreatectomy, and no more recurrence of hypoglycemia was noted. The pathologic examination confirmed the diagnosis of nesidioblastosis.

The clinical presentation of the patient with neurolglycopenia is typical of hyperinsulinemic hypoglycemia, and insulinoma is the most common cause of such a presentation. Nesidioblastosis, accounting for 2 to 18% of hyperinsulinemic hypoglycemia [13], cannot be distinguished from insulinoma based only on clinical presentation. In some cases, nesidioblastosis has been found to be associated with insulinoma [14]. Our review of the literature of the past 10 years found that, while nesidioblastosis was the most common cause of hypoglycemia in infancy, it could occur at any age with equal distribution in both sexes in adults [4]. The rarity of the diagnosis in adults may be related to underdiagnosis, since nesidioblastosis has been accidentally found in autopsies of previously asymptomatic patients [15]. The reported age distribution has ranged from 23 to 84 years. Some cases had a past history of diabetes mellitus [3, 16, 17]. One case report described a patient with morbid obesity who presented with diabetic ketoacidosis at the age of 43 years, but profound hypoglycemia without insulin administration developed at the age of 49 years [16]. Various presentations have been described. A 40-year-old Caucasian man presented with hypoglycemia, severe bradycardia, and ST-T changes on electrocardiogram. Sudden cardiac death ensued and the autopsy revealed only nesidioblastosis, with an organically normal heart and no evidence of cardiomyopathy or CAD [18].

The mechanism of nesidioblastosis in adults is unknown [3]. The presence of focal intraarterial thrombosis and fat necrosis on pathologic examination of the pancreas in our patient suggest the existence of ischemic infarction. Our patient also had histories of CVA and CAD, thus focal infarction of the pancreas might have occurred in the same process of systemic arteriosclerosis. The nesidioblastosis in our patient may have arisen from the exorbitant proliferation of islet cells secondary to the ischemic stress endured in the pancreas.

The treatment of choice for both insulinoma and nesidioblastosis is surgical resection. Histologic evaluation is necessary to confirm the diagnosis since the pancreas may be grossly normal in appearance. The typical pathologic findings of nesidioblastosis include proliferation of islet cells budding from the pancreatic ductules and islet cells within intralobular septae. The pathologic picture in our patient is shown in Fig. 3. The extent of pancreatectomy necessary in the treatment of nesidioblastosis is still disputed. A lesser degree of pancreatectomy is associated with more recurrence of hypoglycemia, but too extensive pancreatectomy complicates the course, with a higher rate of overt diabetes [3, 19–21]. Before operation, medical therapy with diazoxide and/ or somatostatin or its analogue may be tried. If the clinical response to medical therapy is good, then 80% pancreatectomy may be adequate. If the clinical response proves unsatisfactory, more than 90% or near-total pancreatectomy may be considered [21]. In our patient, hypoglycemia resolved postopera-
tively without use of these drugs. The greater age of our patient emphasizes the great benefit of surgery in such cases. The reported cure rate by pancreatectomy is about 80% [2–4, 14, 20, 21], including a case of combined insulinoma and nesidioblastosis. In the other cases with recurrent hypoglycemia after surgery, either medical treatment with diazoxide or somatostatin, or reoperation with near-total pancreatectomy, has been carried out with various success rates.

References