Pancreatic Insulinoma Misdiagnosed as Epilepsy for Eight Years: A Case Report and Literature Review

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Abstract

A 58-year-old Chinese man presented with intermittent seizure episodes after being misdiagnosed with epilepsy for eight years. MRI revealed an abnormally strong signal in the distal pancreas. The patient was subsequently diagnosed with pancreatic insulinoma based on the histological findings, and his symptoms improved following surgical removal of the tumor. The appearance of unusual manifestations of insulinoma makes it difficult to diagnose the condition. This disorder should be included in the differential diagnosis of epilepsy and mental illness.

Key words: insulinoma, hypoglycemia, epilepsy

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Introduction

Pancreatic insulinoma is a common cause of hypoglycemia resulting from endogenous hyperinsulinism. Approximately 90-95% of the tumors are solitary and benign, and the clinical symptoms disappear after complete resection. Clinically, it is often difficult to diagnose insulinoma with atypical symptoms. Therefore it is important to consider the potential for pancreatic insulinoma, particularly in patients presenting with fasting hypoglycemia associated with some degree of central nervous system dysfunction, such as abnormal behavior or confusion.

Confirming the diagnosis of pancreatic insulinoma remains challenging despite improvements in both histological and imaging techniques. In most cases, the diagnosis is made postoperatively based on the histological findings.

We herein present a case of pancreatic insulinoma associated with seizures resulting from hypoglycemia. In this report, we describe the details of the diagnosis and treatment of our patient and provide a review of the literature.

Case Report

A 58-year-old Chinese man with a history of intermittent seizures lasting for eight years was referred to our hospital with hypoglycemia in October 2010. His wife noted that his symptoms had first appeared in 2002. The attacks were characterized by a disturbance of consciousness and uncontrollable muscle spasms with twitching and jerking limbs, during which time the patient was unresponsive for up to 10-30 minutes and then recovered spontaneously, with no distortion of the commisures. Based on his symptoms and medical history, he had been diagnosed with epilepsy at another hospital and subsequently received regular treatment with antiepileptic medication consisting of three drugs, including oxcarbazepine, sodium valproate and phenytoin sodium, although his symptoms did not improve. His wife had noticed that the patient’s symptoms improved after eating solid food or fruit; the patient had gained 8 kg of weight over the last eight years. At the end of October 2010, he was referred to the emergency department due to a disturbance of consciousness and incontinence. He was found to have hypoglycemia, with a glucose level as low as 1.22
Following immediate treatment with the intravenous injection of glucose, he was admitted to the endocrinology ward and all three antiepileptic agents were stopped. The patient was not taking any anti-diabetic drugs or insulin and did not report any prior personal or family history of endocrinopathy or other relevant pathologies. A physical examination was unremarkable, except for dim consciousness. His renal and liver functions were normal, with an HbA1c level of 4.2% and normal cortisol and ACTH rhythms. On the first day of admission, the patient’s glucose level was checked with a capillary blood glucose monitor every hour, and, if hypoglycemia was identified, the plasma glucose level and synchronization of insulin were tested three times. In addition, the insulin release index and insulin modified index were calculated; an insulin release index of >0.3 and insulin modified index of >80 were considered diagnostic for insulinoma due to the inappropriate secretion of insulin. Consequently, the results showed hypoglycemia accompanied by an inappropriate high plasma insulin level (insulin release index: 0.48-1.3 and insulin modified index: 234.2-344.07) (Table). The continuous glucose monitoring system (CGMS) (Medtronic MiniMed MMT/7203U) was applied the next day during treatment with a carbohydrate supplement. The data are presented in graphs and charts in Fig. 4, revealing a pattern of glucose fluctuation, particularly nocturnal hypoglycemia. Following therapy with a continuous intravenous glucose drip, the patient’s consciousness returned to normal. Furthermore, CT scanning of the brain was normal, and no interictal epileptic activity was observed on prolonged video EEG monitoring. Magnetic resonance imaging (MRI) of the abdomen demonstrated an enhanced mass in the distal pancreas (Fig. 1). The results of endocrine and MRI examinations suggested a diagnosis of pancreatic insulinoma.

The patient was subsequently transferred to the department of hepatobiliary surgery, where he underwent surgical removal of the tumor. During the operation, inspection and palpation of the pancreas revealed a small, enucleated nodule in a gland in the tail of the pancreas measuring approximately 2 cm. A histological examination confirmed the excision of a benign pancreatic insulinoma (Fig. 2) with a Ki-67 labeling index of 1%, indicating a low risk of malignant behavior. In addition, the tumor was positive for CK-L (CK-Low), SYN (synaptophysin) and insulin (Fig. 3); CK-L is the main tag of the simple and glandular epithelium, SYN is used to identify tumors arising from neural and neuroendocrine tissues and positivity for insulin provides tumorspecific confirmation of the disease. A diagnosis of benign

| Table. The Plasma Glucose and Synchronization of Insulin Levels of the Patient. |
|-----------------------------------------|----------------|----------------|
| Glucose (mmol/L) | 2.1 | 2.37 | 1.64 |
| Insulin (mU/L) | 18.27 | 43.56 | 38.33 |
| Insulin release index | 0.48 | 1.02 | 1.3 |
| Insulin modified index | 234.2 | 344.07 |

*Insulin release index: insulin (mU/L) / glucose (mg/dL)

*Insulin modified index: insulin(mU/L)×100/ glucose(mg/dL)-30

Figure 1. Abdominal MRI revealed a solitary tumor in the distal portion of the pancreas (arrows).

Figure 2. Hematoxylin and Eosin staining of the insulinoma (×200 magnification).
The insulinoma cells were immunoreactive to CK-L (A), insulin (B), synaptophysin (C) and Ki-67 (D) (×200 magnification).

Figure 4. Preoperative glucose profile on continuous glucose monitoring system (CGMS). The results of at least four finger stick blood glucose readings obtained with a standard glucose meter at different times each day were entered into the monitor for calibration (the blue dot indicates the paired meter value, the red dot indicates the unpaired meter value). The data were considered to have met the standard for accuracy when three or more finger stick blood glucose readings matched the results for CGMS, according to the user guide for the solutions software program for CGMS.

Discussion

Pancreatic insulinoma is the most common functioning pancreatic neuroendocrine tumor (PNET), with an incidence of one to five cases per million people per year (1). The autonomous production of an excessive amount of insulin resulting in hypoglycemia is the classical feature of this tumor, and β-cell adenomas do not reduce insulin secretion in the presence of hypoglycemia. The critical diagnostic criterion is the detection of an inappropriately elevated plasma insulin level under conditions of hypoglycemia. The diagnosis of insulinoma requires confirmation of the presence of hypoglycemia, with evidence of inappropriate insulin secretion and the identification of a pancreatic mass on medical
imaging or angiography (2-5). Insulinomas are often benign, and surgical resection is curative in most patients (6).

Clinically, unawareness of hypoglycemia is common in patients with insulinoma due to adaptations to chronic hypoglycemia involving increases in the efficiency of transporting glucose across the blood-brain barrier. The CGMS provides ongoing measurements of the interstitial glucose levels (7) and is especially useful in patients with unawareness and/or frequent episodes of hypoglycemia (8). In the present case, we used a capillary blood glucose monitor and the CGMS to assess the patient’s glucose level and further confirmed his unawareness of hypoglycemia. Therefore, in patients in whom hypoglycemia is suspected, it is relatively efficient to additionally confirm the diagnosis using continuous glucose monitoring.

Many patients with insulinoma present with neurological and psychiatric manifestations that may result in misdiagnosis. Such misdiagnosis is due to several factors (9). First, the symptoms of insulinoma lack specificity and are similar to those of many common neurological and psychiatric disorders. Therefore, the diagnosis of insulinoma may be missed if the glucose level is not checked. Second, the fasting blood glucose level may be normal in some patients due to the pulsatile nature of insulin secretion. Third, hypoglycemia itself is associated with neuroglycopenic and autonomic unawareness. In a retrospective study of 59 patients with histologically confirmed islet cell adenoma, the interval between the onset of symptoms and diagnosis ranged from one month to 30 years, with a median of 24 months (10), and a significant proportion (39%) of the subjects were originally diagnosed with a seizure disorder (10). In the current report, we described a case of pancreatic insulinoma misdiagnosed as epilepsy for eight years in which the patient received antiepileptic drugs for a long period with no improvements in symptoms. Hence, a delay in diagnosis may result in unnecessary treatment for epilepsy or other psychiatric disorders.

In summary, our patient experienced episodes of hypoglycemic seizures induced by a pancreatic insulinoma. Although pancreatic insulinoma is a benign and curable tumor, it can be fatal if misdiagnosed. Because insulinomas share common clinical characteristics with epilepsy and various mental illnesses, this disease should be included in the differential diagnosis of epilepsy and other mental illnesses, and it is therefore important for neuropsychiatrists to be aware of the importance of evaluating the metabolic causes of seizure disorders.

The authors state that they have no Conflict of Interest (COI).

Hong Ma and Xuan-Pu Zhang contributed equally to this work.

References