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Malignant insulinoma: Report of 6 patients and literature review

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Abstract

OBJECTIVE: Patients with malignant insulinoma always present with symptoms of severe hypoglycemia and have poor life expectancy. In addition, inoperable metastatic malignant insulinomas are very difficult to manage. The aim of this report is to present our successful experiences in diagnosis and treatment of this disease in 6 patients.

PATIENTS/METHODS: Six patients (male 2, female 4) with malignant insulinomas were admitted into our hospital. Their clinical histories, including clinical presentations, endocrine evaluations, radiological images, pathological examination and treatments, were reviewed.

RESULTS: The diagnosis of malignant insulinoma combined with liver metastases was confirmed in all patients by endocrine evaluation and radiological images. Patients 1–3 underwent surgical management. The primary and metastasized tumors were completely resected. After successful surgery, no hypoglycemia recurred. Patients 4–6 did not undergo surgery because of systemic disease and poor health. Instead, they were administrated with diazoxide 50 mg Three Times a Day (TID), with final doses up to 200–300 mg TID. These 3 patients had good responses to diazoxide administration. After treatment, the frequency and severity of hypoglycemia were improved significantly. All 6 patients had better life quality than previously expected.

CONCLUSION: Combination of surgical and medical approaches can improve life quality and prolong survival of patients with malignant insulinomas.

CASE REPORT

INTRODUCTION

Insulinoma is a relatively rare disorder, with approximately four patients per million person-years. Symptomatic hypoglycemia is the major clinical manifestation of insulinomas. Approximately 10–14% of insulinomas are malignant and 7% of them develop metastases. The major metastatic sites are lymph nodes (50%) and liver (70%) (Ferrer-García *et al.* 2013).

Patients with malignant insulinoma always present with persistent and severe hypoglycemia and have poor life expectancy. In addition, the inoperable metastatic malignant insulinomas are very difficult to manage (Roland 2012). Here we present our experiences of diagnoses and treat-

ments with 6 patients with malignant insulinoma combined with liver metastases. Three patients underwent successful operation and the other 3 patients with unresectable lesions received diazoxide regimens. All 6 patients had prolonged their survival.

MATERIALS AND METHODS

Subjects

From 1993 to 2015, six patients with malignant insulinomas were admitted into our hospital. We retrospectively reviewed all their clinical data, including clinical presentations, endocrine evaluations, radiological images, pathological examinations and treatments.

Diagnostic criteria of malignant insulinoma

The diagnostic criteria of malignant insulinoma includes: (1) Patients presented with Whipple's triad: symptoms of neuroglycopenia, documented hypoglycemia, symptoms relief after glucose administration. (2) Inappropriately elevated insulin relaxing index (>0.4(mIU/l)/(mg/dl)) with presence of hypoglycemia was confirmed without other factors such as exogenous insulin or hypoglycemic drugs. (3) Insulinomas or/and metastases could be detected in multiple locations. (4) The malignant insulinomas were further confirmed by pathological examination and immunochemical staining. (5) Hypoglycemia was relieved significantly with a complete tumor resection or appropriate therapy with diazoxide and other effective medicines.

RESULTS

Patient characteristics

Total 6 patients consistent with above diagnostic criteria were enrolled in this report. Their age range from 19 to 58 years (male 2, female 4) and the course was 1 month – 4 years. All of them had no history of administration with exogenous insulin, hypoglycemic medicines or other drugs which might induce hypoglycemia.

The initial presentations in all patients were typical Whipple's triad, including recurrent anxiety, tremor, nausea, hunger, sweating and palpitations. When they were not able to eat any food, drink sugar water, or get medical care, their symptoms progressed into serious neuroglycopenic symptoms, such as seizures, confusion or unconsciousness.

Laboratory examination and radiological imagine

All 6 patients had inappropriately elevated insulin relaxing index (0.79±0.19, normal range <0.3 (mIU/l)/(mg/dl)) with documented hypoglycemia.

Computed tomography (CT), magnetic resonance imaging (MRI), or contrast-enhanced ultrasonography (CEUS) combined with Digital subtraction angiography (DSA) detected lesions in pancreas and multiple metastases in liver in all patients. The typical positive findings of lesions were highly vacularized, compared with surrounding tissues.

Diagnosis and therapy

The diagnosis of malignant insulinoma combined with liver metastases was confirmed in all patients by endocrine evaluation and radiological images.

Patients 1–3 underwent surgical management. The malignant tumors in pancreas and liver metastases were completely resected. After successful surgery, no hypoglycemia recurred. Patients 4–6 underwent liver biopsy. Because of their systemic disease and poor health, patients 4–6 could not undergo surgery. Liver biopsies were performed. Pathological and immunohistochemical analyses of biopsy tissues confirmed malignant insulinomas in these patients (Figure 1, 2). They were treated with diazoxide at 50 mg Three Times a Day (TID), with final doses up to 200–300 mg TID. These patients responded well to diazoxide. The fre-

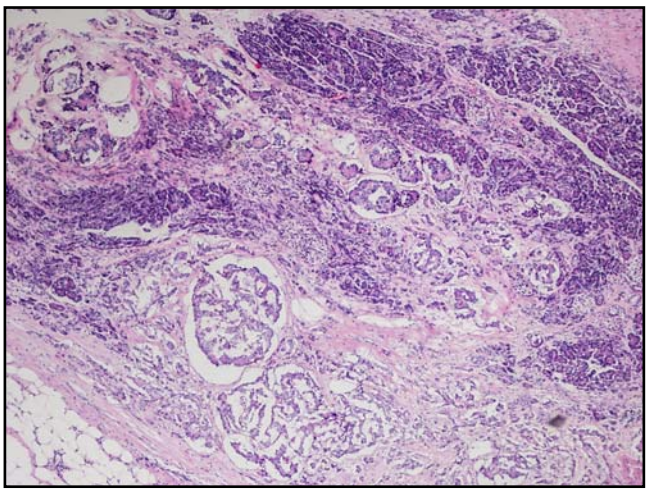

Fig. 1. Histological examination of the original pancreatic tumor in patient 3 reviewed alveolar tumor infiltrate within and around the normal pancreatic acinus – H & E (×40).

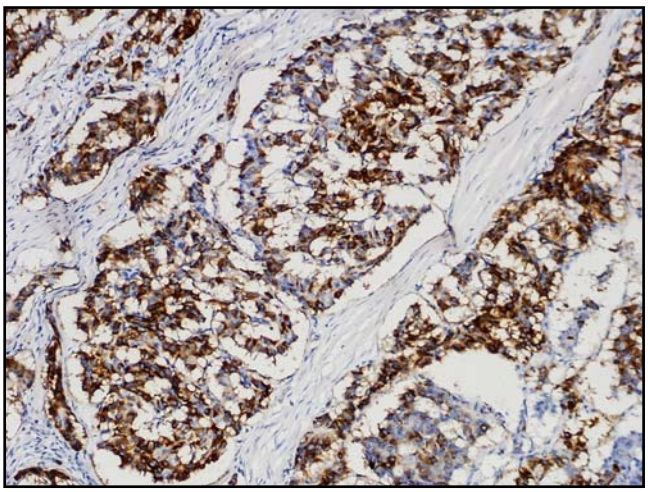

Fig. 2. The cytoplasm of pancreatic tumor in patient 3 was strongly immunoreactive (Brown) for insulin (×200).

quencies and severity of hypoglycemia were significantly reduced in all 6 patients after either the surgical or medical treatment and their quality of life was clearly improved.

DISCUSSION

When patients with recurrent symptomatic hypoglycemia look for medical care, as the patients in this report, the possibility of insulinoma should be seriously considered.

During diagnosis, Whipple's triad should be determined first. The symptoms include: (1) symptoms of neuroglycopenia; (2) documented hypoglycemia (plasma glucose levels <50 mg/dl) and (3) symptoms relief (often within 10 minutes) following glucose administration. Once the Whipple's triad is confirmed, plasma insulin levels should be checked. An inappropriately elevated insulin relaxing index (>0.4 (mIU/l)/(mg/dl)) with the presence of hypoglycemia strongly indicates the presence of insulinoma after other factors, such as administration of exogenous insulin or hypoglycemic drugs are ruled out. All patients in our report initially presented with recurrent symptoms of neuroglycopenia. After admission, the serious hypoglycemia and hyperinsulinemia were confirmed at the time of the episodes. Insulin relaxing indexes in these patients were 0.79±0.19 (mIU/l)/(mg/dl)), significantly higher than the normal level which is 0.4 (mIU/l)/(mg/dl)). Therefore, the diagnosis of insulinoma was confirmed.

Insulinomas are rare tumors which arise from pancreatic islet cells. Benign insulinomas are typically solitary pancreatic lesions that are small (90% less than 2 cm), well circumscribed and equally distributed throughout the pancreas (head, body, and tail). Approximately 7% of insulinomas are malignant. Malignant insulinomas are usually much larger than benign ones and may metastasize to multiple locationsin the liver. Sometimes, metastases are the main evidence of malignant insulinomas.

Due to its typical clinical presentations and biochemical tests, the pancreatic insulinoma, benign or malignant, could be quickly diagnosed. The location of the tumor could be determined with various imaging techniques, including invasive and non-invasive procedures.

Preoperative localization is necessary for the successful operation of insulinomas. A combination of routine non-invasive imaging techniques, including ultrasonography (US), computerized tomography (CT) and magnetic resonance imaging (MRI), are conventionally used to locate larger insulinomas. However the method is usually unable to detect insulinomas smaller than 1cm (Varma *et al.* 2011).

Invasive techniques, such as digital subtraction angiography (DSA), transhepatic portal-venous sampling (THPVS), endoscopic US (EUS), and intraoperative US have advantages in localization of small insulinomas. Some of them are usually employed if all non-invasive imaging procedures fail. Intraoperative US (IOUS) is capable of showing the relevant operative anatomy, defining the relationship of the tumor to surrounding tissues and adjacent blood vessels. Therefore, it is a useful and reliable technique in locating insulinomas and determining surgical procedures, especially when multiple lesions are to be suspected. In this report, we used CT, MRI, CEUS and DSA to successfully locate lesions in the pancreas, and detect multiple lesions in the liver in all patients. These identified lesions were later confirmed by either operation or biopsy.

Additionally, malignant insulinomas typically show frequent expressions of somatostatin receptor subtype 2/5. As a result, Somatostatin receptor scintigraphy (SRS) is a useful method for localizing malignant insulinomas. ^{18}F-fluorodeoxyglucose (18 F-FDG) PET imaging is a promising technique in detecting malignant insulinomas, especially multiple metastases in surrounding tissues due to the high proliferative potential of tumor cells (Ambrosini *et al.* 2015).

Malignant or metastatic insulinoma is a rare but serious condition. Patients with malignant insulinoma usually had advanced disease at the time of diagnosis and poor life expectancy. There are two challenges to clinicians. The first is to successfully resect the malignant insulinoma, solidary or multiple, with or without metastases. The second is to control severe hypoglycemia in patients with unresectable malignant insulinomas. So multimodal therapeutic interventions should be applied to these patients (Hagel *et al.* 2011).

It is obvious that when insulinoma is confirmed with proper locating techniques, the surgery for tumor removal is the first course of tumor management. The advantages of laparoscopic surgery are well established and the technique applied in many intraabdominal conditions. Curative surgery encompasses radical removal of the primary, for example, pylorus-preserving duodeno-pancreatic resection, distal pancreatectomy, lymphadenectomy, and removal of resectable liver metastases. In unresectable hepatic or systemic disease, palliative tumor debulking may be justified to achieve hypoglycemic control and may prolong patients' survival (Crippa *et al.* 2012; Guo *et al.* 2013). Patient 1–3 underwent surgery and the malignant insulinoma and metastases in liver were completely resected. Patient 4–6 could not undergo surgery. Instead, liver biopsies were performed. The pathological and immunohistochemical evaluation on tumor tissues confirmed the malignant insulinoma and liver metastasis lesions in these patients.

It is usually difficult to control abnormal insulin secretion and hypoglycemia in patients with malignant insulinomas, especially with multiple metastases or unresectable malignant insulinomas. In our case, we treated Patients 4–6 with diazoxide.

The most effective drug for controlling hypoglycemia is diazoxide (50–300 mg/day, up to 600 mg/day).

Diazoxide is an antihypertensive benzothiadiazine derivative without diuretic activity. However it can induce hyperglycemia. Potential glycaemic mechanisms include suppressing of glucose and adrenergically mediated insulin release, or increasing hepatic gluconeogenesis. Its side effects include edema, weight gain, renal impairment and hirsutism (de Herder *et al.* 2011). We have found that a small initial dose with an increase to 300–400 mg per day over 3–4 weeks is the most effective way to treat hyperglycemia. In our report, patients 4–6, who could not undergo surgery, had good responses to diazoxide treatment. Their hypoglycemia was well controlled and all the adverse effects could be tolerated, life quality was improved and their life expectancy was prolonged.

Somatostatin is an inhibitor of pancreatic insulin and glucagon release mediated through G-protein trans-membrane receptors. Octreotide is a somatostatin analog which affects the somatostatin receptors (SSTRs), with a strong affinity for SSTR2 and SSTR5 isoforms. This medicine can inhibit insulin or proinsulin secretion from insulinomas as well as the growth of insulinoma cells. So it is effective in controlling recurrent and serious hypoglycemia in patients with malignant insulinoma (Maiza *et al.* 2011). Recently, it is reported that Sandostatin LAR 10–20 mg monthly can improve fasting blood glucose and serum insulin in unresectable metastatic malignant insulinomas for up to 3 years, which is more effective than octreotide. The blood concentration of octreotide LAR was more appropriate and stable, compared with octreotide treatment, and coud decrease the insulin level to an appropriate range, thereby achieving and maintaining euglycaemia after the initiation of octreotide LAR treatment (Okamoto *et al.* 2013).

The mechanistic target of rapamycin (mTOR) is a key intracellular component of signaling pathways responsible for cell growth and survival. Dysregulations of upstream components upregulate mTOR, making it a potential target for anti-tumor therapy. mTOR receptor inhibitors rapamycin (sirolimus) and everolimus can cause hyperglycemia through complex mechanisms inducing hepatic and peripheral resistance to insulin as well as β-islet cell toxicity. It has been reported that treatment of patients with sirolimus (rapamycin) 2 mg daily reduces the size of multiple malignant insulinomas and refractory hypoglycemia and can even allow withdrawal or reduction in the use of diazoxide, octreotide and iv dextrose. Therefore, application of mTOR inhibitors early in hypoglycemia refractory to conventional therapy could be considered (de Herder *et al.* 2011).

Although metastatic insulinoma is a disease associated with a poor life expectancy, combination of aggressive multimodal therapy as discussed above could improve patients' survival (Ong *et al.* 2010; Muro *et al.* 2014).

CONCLUSION

In the current study, 6 patients with persistent and severe hypoglycemia were confirmed to have malignant insulinomas combined with liver metastases. Three patients had the all the lesions successfully resected. Another 3 patients with unresectable lesions were administrated with diazoxide. After successful therapy, the recurrent and serious hypoglycemia was improved in all these 6 patients, which lead to better life quality and prolonged survival than previously expected.

Conflict of interest statement

The authors have no conflict of interest to declare.

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