Clinical case

Malignant insulinoma misdiagnosed and treated as epilepsy

Insulinome malin mal diagnostiqué et traité comme épilepsie

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Abstract

Pancreatic neuroendocrine tumors (PNET) are extremely rare, and although insulinomas are the commonest, less than 10% of insulinomas are malignant. Most patients with insulinomas present neuroglycopenic symptoms. Because of the rarity of the condition, we report the case of a 56-year-old man with malignant insulinoma, which was misdiagnosed as epilepsy. Timely diagnosis of this disease is of paramount importance to prevent neurologic sequelae of hypoglycemia. Insulinomas should be regarded from the beginning as potentially malignant, although the majority of malignant insulinomas progress slowly.

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Résumé

Les tumeurs neuro-endocrines du pancréas (TNE) sont extrêmement rares, et bien que les insulinomes soient les plus fréquents, moins de 10 % des insulinomes sont malins. La plupart des patients ayant un insulinome présentent des symptômes neuroglycopeniques. En raison de la rareté de la maladie, nous rapportons le cas d’un homme de 56 ans avec insulinome malin qui était diagnostiqué et traité à tort comme épilepsie. Le diagnostic précoce de cette maladie est d’une importance primordiale pour éviter des séquelles neurologiques d’hypoglycémi. L’insulinome doit être considéré dès le début comme potentiellement malin, bien que la majorité progresse lentement.

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1. Introduction

Insulinoma is a rare tumor, most of them are benign, but some are malignant and have a potential for metastases. The disease should be considered in patients presenting episodic adrenergic and/or neuroglycopenic symptoms of hypoglycemia, which might be misdiagnosed as neurologic disorder such as epilepsy. Toxic and metabolic causes of neurologic disorder should always be considered as they are curable, and may be fatal if untreated.

The following case report highlights importance of considering hypoglycemia in atypical neurological or psychiatric episodes.

2. Case report

A 56-year-old man was referred to the hospital. The personal history was unremarkable. He presents, 4 years before his admission, discomfort with shaking and sometimes loss of consciousness. He had been diagnosed as epilepsy and commenced on antiepileptic medication. Despite treatment, his crises frequency and pattern had worsened significantly during the previous 4 years.

Laboratory tests done with a concomitant crisis showed blood glucose 0.33 g/L.

The patient was sent to the endocrinology department for assessment of this hypoglycemia. On examination, these discomforts are preceded by palpitation, sweating, tremors, shaking and, sometimes, loss of consciousness.

These attacks occur between meals, fasting, or during physical effort, and yield to sugar intake. There is a weight gain from 20 kg in 4 years. General examination was unremarkable.

After 6 hours of fasting: blood glucose level was less than 33 mg/dL (reference range: 60–110 mg/dL). Both basal insulin and C-peptide serum levels were 15.51 μU/mL (reference range: 2–17 μU/mL) and 3.85 ng/mL (reference range: 1.15–4.5 ng/mL), respectively. An abdominal CT-scan showed a large pancreatic body solid mass of about 20 cm in diameter, without other abnormalities (Fig. 1). Endoscopic ultrasound
Fig. 1. Abdominal CT-scan showed a pancreatic body solid mass of about 21 mm in diameter, enhancing strongly after injection, without other abnormalities.

showed a pancreatic tail mass of about 6 mm. Surgical approach was planned and a body-tail pancreatectomy was performed.

Pathological examination of the specimen showed a solid mass of $2 \times 2 \times 1.5$ cm in diameter (Fig. 2). Surgical margins were tumor free with capsular intrusion and vascular intra-capsular emboli and Ki-67 was less than 2%. Tumor cells displayed diffuse positivity for chromogranin. A final diagnosis of well-differentiated pancreatic endocrine carcinoma, histological grade 2 (G2), pT2, was performed. The postoperative course was uneventful, disease-free with a good control of blood glucose level at 2 months after surgery. Assessment of lesions MEN-1: serum calcium is normal and brain MRI is normal, the complement of the review is under way.

3. Discussion

Insulinomas are the most common functioning endocrine tumors of the pancreas, with an estimated incidence of 1 to 3 per million per year, an age-specific incidence peak in the fifth decade of life, there is a female predominance. Tumors are usually solitary, small, benign, and sporadic [1]. Approximately 10% are multiple. Less than 10% can be malignant [2] and 4% are associated with the MEN-1 syndrome [3]. Insulinomas present with symptoms of hypoglycemia, especially neuroglycopenic and adrenergic symptoms, which are worsen by fasting [2]. The presence of Whipple’s triad remains fundamental. An international review of 1067 cases [3] showed neuropsychiatric symptoms in 92% of the patients, such as loss of consciousness, confusion, asthenia, deep coma, dizziness, and epilepsy.

As seen in our case, initial misdiagnosis is frequent. The median interval from the onset of symptoms to the diagnoses of insulinoma is 2 years, with a wide range of 1 month to 30 years [4]. Diagnosis relies on inappropriate insulin and C-peptide secretion in the presence of hypoglycemia and subsequent tumor localization.

Localization of insulinomas may be difficult because they are often small in size. The role of imaging is to detect and provide precise anatomical localization and staging of tumors prior to surgery and during follow-up [5]. Conventional imaging studies detect more than 70% of pancreatic neuroendocrine tumors (PNET) that are greater than 3 cm, they detect less than 50% of most PNET that are less than 1 cm, therefore frequently missing small primary PNET (especially insulinomas, duodenal gastrinomas) and small liver metastases [6]. In these situations, somatostatin receptor scintigraphy (SRS), combined with CT [7], and endoscopic ultrasound [8] are helpful. Interest of positron emission tomographic scanning is limited in the insulinoma [9]. Intraoperative ultrasonography may be able to localize small insulinomas, which cannot be detected by palpation, in a range of 83 to 90% [10].

Concerning histological features, WHO adopted a new classification of endocrine tumors of the pancreas based on clinical and pathological criteria. Ki-67 is an index of proliferative status, suggesting a more aggressive behavior when it is greater
Grading of pancreatic neuroendocrine tumors (PNET) including insulinomas.

<table>
<thead>
<tr>
<th>Grade</th>
<th>ENTES</th>
<th>WHO 2010</th>
<th>Differentiation</th>
<th>Ki-67 index (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low grade</td>
<td>NET grade 1 (G1)</td>
<td>Neuroendocrine neoplasms grade 1</td>
<td>Well differentiated</td>
<td>&lt;2</td>
</tr>
<tr>
<td>Intermediate</td>
<td>NET grade 1 (G1)</td>
<td>Neuroendocrine neoplasms grade 2</td>
<td>Well differentiated</td>
<td>2–20</td>
</tr>
<tr>
<td>High grade</td>
<td>Neuroendocrine carcinoma grade 3 (G3)</td>
<td>Neuroendocrine neoplasms grade 3</td>
<td>Poorly differentiated</td>
<td>&gt; 20</td>
</tr>
<tr>
<td>High grade</td>
<td>Small cell carcinoma</td>
<td>Small cell carcinoma</td>
<td>Poorly differentiated</td>
<td>&gt; 20</td>
</tr>
</tbody>
</table>

ENTES: European neuroendocrine tumor society.

than 2% [11]. In our patient, it is less than 2%. Still, the diagnosis of neuroendocrine carcinoma may be established only in the presence of metastases and/or invasiveness. The WHO classifies functioning endocrine tumors of the pancreas into three well-defined categories (Table 1) [12,13]. For staging and grading of insulinomas, current WHO, ENETS guidelines for PNET are used (Table 1) [13–15].

In patients with neuroendocrine tumors, we should always search for MEN-1 which represent a syndrome inherited as an autosomal dominant trait, and include: hyperparathyroidism (95%), enteropancreatic tumors (30–80%), pituitary adenomas (most frequent prolactinoma, followed by growth hormone secreting tumors; 20–25%), carcinoid tumors (20%), adrenal adenomas (40%) and subcutaneous lipomas (30%) [16].

Surgical resection is the treatment of choice [16]. Dietary modification with frequent small feedings may help control the hypoglycemia. Diazoxide (200–600 mg/day) successfully controls hypoglycemia in 50% to 60% of patients [17]. Long-acting somatostatin analogs control hypoglycemic symptoms in up to 50% of patients with non-metastatic insulinomas; however, in some cases, they may worsen the hypoglycemia [18].

In malignant insulinomas, surgery represents the only curative option, although this is rarely possible, and medical therapy is always required in patients in addition to surgery or in patients with inoperable disease [19].

Following-up after surgery [20] has goal to provide a curative treatment, mainly surgery, when lymph node recurrence or metastatic hepatic or other. In situations with low risk of recurrence, ultrasonography is an inexpensive alternative. In other situations, CT-scanning and MRI should be preferred. No biological marker is validated in follow-up.

Disclosure of interest

The authors declare that they have no conflicts of interest concerning this article.

References