Caso Clínico

Hipercalcitoninemia e Insulinoma: Uma Rara Associação

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INFORMAÇÃO SOBRE O ARTIGO

Historial do artigo:
Received/ RECEBIDO: 2019-10-19
Accepted/A CEITE: 2020-04-06
Online: 2020-07-08

Palavras-chave:
Calcitonina;
Insulinoma;
Neoplasias Pancreáticas;
Tumores Neuroendócrinos.

Hypercalcitoninemia and Insulinoma: A Rare Association

A calcitonina é um marcador bioquímico crucial utilizado na monitorização de pacientes com diagnóstico de carcinoma medular da tiroide. Contudo, níveis aumentados de calcitonina podem também ocorrer noutras condições clínicas, nomeadamente em tumores neuroendócrinos pancreáticos. A incidência da secreção de calcitonina por estes tumores é desconhecida. Apresentamos o caso de um homem de 72 anos com um quadro caracterizado por episódios de lipotêmias, parestesias das mãos e boca, associados a hipoglicémias graves pré-prandiais. A marcha diagnóstica revelou um insulinoma com imunomarcação para a calcitonina. É de salientar que uma hipercalcitoninemia subjacente foi detetada. Adicionalmente, fizemos uma revisão dos casos semelhantes, reportados na literatura. O presente caso destaca uma causa rara de hipercalcitoninemia e a necessidade de compreender melhor as implicações da secreção de calcitonina pelos tumores neuroendócrinos pancreáticos.

Keywords:
Calcitonin;
Insulinoma;
Neuroendocrine Tumors;
Pancreatic Neoplasms.

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Revista Portuguesa de Endocrinologia, Diabetes e Metabolismo

www.spedmjourn.com

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https://doi.org/10.26497/cc190049
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Introduction

Pancreatic neuroendocrine tumours (PanNET) include a rare group of neoplasms that arise from multipotent neuroendocrine cells with the ability to synthesize, store and secrete specific peptide hormones. These tumours can be classified as functioning (FPanNET), based on the presence of distinct clinical syndromes inherent to the secretion of biologically active substances that can be detected in serum. Some of these molecules can be detected by immunohistochemistry. The metabolic products can be inactive or produced at low levels with no obvious symptoms attributed to peptide hormone hypersecretion. If the tumour is not functional (clinically) one can forgo the immunostains for functional tumours. In this case, these tumours are classified as non-functioning (NFPanNET). PanNET account for 1%-2% of pancreatic neoplasms, of which 50% are functional (FPanNET). Insulomas are the most common type of FPanNET, corresponding to 17% of cases, with an annual incidence of 4 per 1 million person-years. Insulomas produce insulin and usually have an indolent course, presenting with signs and symptoms of hypoglycaemia. PanNETs may have multi-hormonal immunoreactivity/secretion. Besides eutopic hormonal secretion (insulin, glucagon, pancreatic polypeptide), PanNET may rarely produce non-pancreatic hormones ectopically (ACTH, GHRH, PTHrP, neurotensin, calcitonin, ghrelin, etc.). There are few reports in the literature of functioning calcitonin-secreting PNETs, and only 5 case reports of calcitonin secreting insulomas. We describe a case of a 72-year-old man with an insuloma secreting calcitonin, and perform a review of the related literature.

Case Report

A 72-year-old caucasian man, without remarkable past medical and family history was referred to our endocrinology clinic for evaluation of hypoglycaemias. He had history of intermittent episodes of lipothyrmia and paraesthesias of the hands and mouth in the previous 8 months that improved with food ingestion. The patient performed self-monitoring of blood glucose which revealed severe hypoglycaemias before meals, mainly in the fasting state (Table 1). There was no use of any medications. The laboratory findings during a spontaneous episode of hypoglycaemia revealed a glycaemia of 42 mg/dL, an inappropriately high level of plasma insulin of 30.6 mU/L [reference range (RR) 2-25] and of C-peptide of 4.04 nmol/L [RR 0.8-3.5], a high pro-insulin value of 65.6 pmol/L [RR <5.1] and a normal β-hydroxybutyrate level. An increased of basal plasma glucose after administration of 1 mg of intravenous glucagon was observed (10’ 78 mg/dL, 20’ 118 mg/dL and 30’ 110 mg/dL). Hyperinsulinaemic hypoglycaemia was thus confirmed. Glycated haemoglobin was 5.1%. An increased of basal calcitonin level of 149 pg/mL [RR <3] and neuron specific enolase (NSE) 20.8 ug/L [RR < 16] was observed. Anti-insulin and anti-insulin receptor antibodies were negative. Serum calcium, parathormone and 25-hydroxyvitamin D levels were normal. As also other hormonal studies including thyroid function, adrenocorticotropic hormone (ACTH), serum cortisol level, IGF1, prolactin were normal. Other hormonal studies including thyroid function, adrenocorticotropic hormone (ACTH), serum cortisol level, IGF1, prolactin were normal. A thyroid ultrasound revealed a microcyst in the right thyroid lobe. Magnetic resonance imaging (MRI) of the abdomen revealed a nodular image with 17 mm, characterized by discrete arterial enhancement, diffusion restriction, hyperintense signal on T2-weighted image and low signal intensity in T1-weighted image, suggestive of an insulinoma (Fig. 1). No evidence of lymph nodes or distant metastasis were detected. An endoscopic ultrasonography guided fine-needle-aspiration biopsy of the 20.3 mm lesion showed a neuroendocrine tumour. While on surgery waiting list, the patient was advised to do frequent meals; diazoxide treatment was started (100 mg three times daily, increasing up to 150 mg three times daily). However the patient developed fluid retention mainly in the lower limbs, which led to the discontinuation of the drug. He underwent laparotomy, the tumour was localized by palpation in combination with intraoperative ultrasonography. A pancreaticoduodenectomy/partial pancreatectomy (Fig. 2), with appendectomy and cholecystectomy were performed. In the gross section of pancreatic head, we identified an intraglandular solid tumour, measuring 22x20x18 mm,

| Table 1. Daily blood glucose (mg/dL) recording of the patient. |
|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|---------------------------------|
| Breakfast | Lunch | Afternoon snack | Dinner | At bedtime |
| Before | After | Before | After | Before | After | Before | After | Before |
| 46 | 62 | 38 | 100 | 60 | 162 | 68 | 120 | 72 |
| 40 | 91 | 37 | 98 | 56 | 160 | 72 | 140 | 76 |
| 42 | 90 | 33 | 96 | 42 | 142 | 71 | 142 | 71 |
| 30 | 102 | 36 | 102 | 46 | 154 | 80 | 160 | 78 |
| 36 | 94 | 34 | 89 | 37 | 136 | 74 | 168 | 70 |
A surgical specimen from pancreaticoduodenectomy/partial pancreatectomy of insulinoma in the uncinate process of the pancreas.

Discussion

Calcitonin is mainly expressed by parafollicular cells or C cells of the thyroid. The role of calcitonin is not fully understood. This hormone seems to contribute to calcium homeostasis. It lowers serum calcium by inhibiting osteoclast activity, playing a minor role in the regulation of bone turnover. Moreover calcitonin decrease tubular reabsorption of calcium, promoting renal excretion. In clinical practice it represents a sensitive marker for pre-operative diagnosis and post-surgical follow-up of medullary thyroid carcinoma (MTC), however elevated levels of this hormone are not pathognomonic of MTC. Ectopic calcitonin secretion may occur in certain benign clinical conditions such as chronic renal disease, sepsis, autoimmune thyroiditis, mastocytosis, hypercalcemia, hypergastrinemia and may be rarely secreted ectopically by extra thyroidal tumours - NETs (pheochromocytomas, paragangliomas, larynx, lung and gastrointestinal NETs), adrenal carcinomas, lung, breast, prostate, and colorectal carcinomas. In the present case we evaluated calcitonin levels once we suspected of a FPanNET. There are some reports in the literature of both operational and non-functioning calcitonin–secreting PanNETs. The exact incidence of calcitonin expression in these tumours is unknown. Uccela S et al performed a review of the literature and found a predominance of calcitonin-immunoreactive VIPomas among FPanNETs, contrary to what the authors found in their own study, in which insulinomas predominated. In the English and French literature we found 5 cases of calcitonin-secreting insulinomas. In one case of a sporadic insulinoma, an abnormal karyotype was found involving chromosome 1p13 region ( locus of N-Ras and Krev-1, a proto-oncogene and tumour suppressor genes respectively). Nevertheless, common chromosomal abnormalities have not been identified. Among PanNET with isolated secretion of calcitonin, none were associated with a specific syndrome. In some of the reported cases of calcitonin–secreting PanNET, calcitonin was requested in the context of nodular thyroid disease. In others no thyroid disease was identified, leading to unnecessary total thyroidectomies due to the suspicion of a small MTC. In some case reports, calcitonin–secreting PanNET were diagnosed due to systemic or gastrointestinal symptoms (diarrhoea, abdominal pain, etc.) and the presence of a suspected image on CT scan or abdominal ultrasound. It appears that serum values of unstimulated calcitonin greater than 100 pg/mL are more suggestive of a MTC. However, some case reports calcitonin-secreting insulinomas had serum calcitonin levels above 100 pg/mL. Moreover Schneider et al found that PanNETs induced an average in serum calcitonin increase of 89.2 times the upper limit of normal. An increase in the serum value of calcitonin five to ten times after the pentagastrin stimulation test may be lower or even absent in the presence of ectopic calcitonin compared to MTC. Some of the calcitonin – secreting PanNETs reported presented with hepatic metastasis. Schneider et al reported metastasis (mostly hepatic) in 59.7% of calcitonin - se-
In conclusion, probably the secretion of calcitonin by functional PanNETs raises the question whether the secretion of calcitonin by these tumours remains unknown and is left out, a PanNET should be evoked. The clinical importance of calcitonin secretion by these tumours remains unknown and should be addressed in future studies.

It is worth to mention that we did not perform genetic screening for multiple endocrine neoplasia in the present case. Although very low, benign insulinomas are not devoid of recurrence. We consider the patient should be periodically evaluated for symptoms of hypoglycaemia and calcitonin may play a role as biochemical marker. It is worth to mention that we did not perform genetic screening for multiple endocrine neoplasia in this patient given the patient’s age, the absence of family history for MEN syndrome and the clinical presentation with isolated insulinoma. The genetic screening for MEN1 is well established: it is recommended in the presence of family background of MEN1 or if there are grounds for suspecting of MEN1 diagnosis (e.g., multiple parathyroid tumours, gastrinoma, or multiple pancreatic neuroendocrine tumours). Regarding RET germline mutations, testing is recommended in cases of a personal history of medullary thyroid carcinoma, primary C-cell hyperplasia or pheochromocytoma.24–32

In probability, the secretion of calcitonin by functioning and non-functioning PanNETs is more frequent than is thought. The calcitonin measurement in this patient was performed in the context of a suspected neuroendocrine tumour namely an insulinoma. The role of this secretion in PanNETs should be addressed in future studies.

**Table 2.** Clinicopathological features of isolated case reports of calcitonin-secreting insulinomas.

<table>
<thead>
<tr>
<th>Case report</th>
<th>Age</th>
<th>Sex</th>
<th>Clinical presentation</th>
<th>Serum Insulin levels</th>
<th>Serum Peptide -C levels</th>
<th>Serum Calcitonin levels</th>
<th>Type of Surgery</th>
<th>Site</th>
<th>Size (mm)</th>
<th>Ki67</th>
<th>Im. St. (Calcitonin/Insulin)</th>
<th>Im. St. (other hormones)</th>
<th>Metastasis</th>
<th>Serum calcitonin/Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ooi et al (1986)</td>
<td>67</td>
<td>M</td>
<td>Hypoglycaemia</td>
<td>18.6 mU/L (&lt;16)</td>
<td>1.04 nmol/l (0.2-0.63)</td>
<td>0.34 µg/l (&lt;0.08)</td>
<td>Laparotomy</td>
<td>Un</td>
<td>Un</td>
<td>15</td>
<td>Calcitonin Insulin</td>
<td>Un</td>
<td>Un</td>
<td>Un</td>
</tr>
<tr>
<td>Price et al (1992)</td>
<td>42</td>
<td>F</td>
<td>MEN1</td>
<td>653 pmol/l (35-145)</td>
<td>0.96 nmol/l (0.17-0.66)</td>
<td>14.4 pmol/l (&lt;2.9)</td>
<td>DP</td>
<td>B/T</td>
<td>12</td>
<td>Calcitonin Insulin</td>
<td>Gastrin</td>
<td>No</td>
<td>0.14 µg/l (&lt;0.08) Dead after surgery</td>
<td></td>
</tr>
<tr>
<td>Gaulier et al (1993)</td>
<td>58</td>
<td>F</td>
<td>Hypoglycaemia</td>
<td>Fasting hypoglycaemia</td>
<td>Diarrhoea Dyspepsia</td>
<td>88.08 µU/mL (5-35)</td>
<td>Pancreatic head resection</td>
<td>H</td>
<td>25</td>
<td>10%</td>
<td>Calcitonin Insulin</td>
<td>Synaptophysin</td>
<td>NSE C peptide Proinsulin</td>
<td>No</td>
</tr>
<tr>
<td>Bugalho et al (1994)</td>
<td>71</td>
<td>F</td>
<td>Fasting hypoglycaemia</td>
<td>481 pg/mL (9.9)</td>
<td>Pancreatic head resection</td>
<td>H</td>
<td>22</td>
<td>&lt;3%</td>
<td>Calcitonin Insulin</td>
<td>Chr A Synaptophysin</td>
<td>No</td>
<td>2.89 pg/ml (&lt;9.9) Free of disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pusztai et al (2006)</td>
<td>54</td>
<td>F</td>
<td>Fasting hypoglycaemia</td>
<td>30.6 mU/L (2-25)</td>
<td>Duodenopancreectomy</td>
<td>Uncus</td>
<td>22</td>
<td>&lt;3%</td>
<td>Calcitonin Insulin</td>
<td>Chr A NSE Synaptophysin</td>
<td>No</td>
<td>Free of disease</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Chr A, chromogranine A; B/T, body and tail; DP, distal pancreatectomy; F, female; H, head; HR, histopathological examination; Im.St., immunohistochemical staining; M, male; NSE, neuron-specific enolase; Sr serum; T, thyroidectomy; Un, unknown.

**Acknowledgements / Agradecimentos**

We thank to Dr. António Matos for providing complementary information in the interpretation of the MRI. We also thank to Laura Deus for figures edition.

**Responsabilidades Éticas**

**Confliitos de Interesse:** Os autores declaram a inexistência de conflitos de interesse na realização do presente trabalho.

**Fontes de Financiamento:** Não existiram fontes externas de financiamento para a realização deste artigo.

**Confidencialidade dos Dados:** Os autores declaram ter seguido os protocolos da sua instituição acerca da publicação dos dados de doentes.

**Consentimento:** Consentimento do doente para publicação obtido.

**Proveniência e Revisão por Pares:** Não comissionado; revisão externa por pares.

A series of 6 cases revealed that these tumours were often malignant.3 Nozières et al.29 found that 21/176 patients (12%) of calcitonin – secreting PanNETs, had recurrence of the disease after surgery and needed combined adjuvant therapy. This raises the question whether the secretion of calcitonin by these tumours is associated with a worse prognosis. A systematic analysis of 229 PanNET, identified 25 cases with calcitonin-immunoreactivity (10.9%) and concluded that there were no differences in prognosis regarding CT versus non-secreting tumours. In addition, in this study, it was found that calcitonin secreting insulinomas had an equal prognosis to those non-secreting calcitonin, which is in accordance with the present case.26 In Table 2 we identified and reviewed the calcitonin-secreting insulinomas individual case reports that we found in the literature.

Although very low, benign insulinomas are not devoid of recurrence. We consider the patient should be periodically evaluated for symptoms of hypoglycaemia and calcitonin may play a role as biochemical marker.
Ethical Disclosures

Conflicts of Interest: The authors have no conflicts of interest to declare.

Financing Support: This work has not received any contribution, grant or scholarship.

Confidentiality of Data: The authors declare that they have followed the protocols of their work center on the publication of data from patients.

Patient Consent: Consent for publication was obtained.

Provenance and Peer Review: Not commissioned; externally peer reviewed.

References / Referências