Endocrinología, Diabetes y Nutrición 71 (2024) 31–37

Endocrinología, Diabetes y Nutrición

www.elsevier.es/endo

SCIENTIFIC LETTER

Hypercalcemia as the first finding of late recurrence of a PTHrP neuroendocrine tumor of the pancreas

Hipercalcemia como primer hallazgo de recidiva tardía de un tumor neuroendocrino de páncreas productor de PTHrP

Hypercalcaemia is a common condition in cancer patients (20–30%) and is a poor prognostic factor.[1] It is caused by parathyroid hormone-related protein (PTHrP) in 80% of cases. PTHrP can be released by various tumours, such as squamous cell carcinomas, including lung, head and neck, kidney, bladder, ovarian and breast cancer.[1] However, it is extremely rare in gastrointestinal neuroendocrine tumours (NET),[2,3] with a prevalence ranging from 0.47[2] to 1.1%[3] of all NET, according to different series.

We present the case of a patient with a pancreatic neuroendocrine tumour (pNET) in whom hypercalcaemia with suppressed PTH was useful for both initial diagnosis and detection of recurrence.

This was a 40-year-old man who consulted with discomfort in the left hypochondriac region, associated with polyuria, polydipsia and weight loss of 7 kg in the previous two months. Complete blood count showed serum calcium 11.4 mg/dl (8.5–10.2), PTH 6 pg/mL (9–65), Ca 19.9 105.0 IU/mL (0.0–34.0) and neuron-specific enolase (NSE) 57 ng/mL (0–16). PTHrP levels were 6.7 pmol/l (<1.5). Computed tomography showed a multi-lobulated mass measuring 10 × 3 × 8.5 cm in diameter (APxTxL) without continuity with splenic parenchyma, without a fatty plane of separation from the pancreatic tail, with a differential diagnosis of lymphoma or cancer of the tail of the pancreas. Somatostatin receptor scintigraphy was performed with ^{111}In (Octreoscan), which showed hyperuptake, subsequently confirmed by ^{18}F-fluorodeoxyglucose (^{18}FDG) PET, which revealed a suspected malignant tumour with a SUVmax of 8.3. Distal pancreatectomy with splenectomy was performed. Histology reported well-differentiated G2 pNET (Ki-67: 5%), with expression of CKAE1/AE3, CK19 and, intensely and diffusely synaptophysin and CD56, with focal and patchy immunostaining for chromogranin A (CgA).

After surgery, serum calcium levels returned to normal, and laboratory and morphological follow-up was carried out for five years, with all tests normal. Eight years after the procedure, the patient consulted again and blood tests showed serum calcium 10.8 mg/dl, CgA 75 ng/mL (0–102) and NSE 14 ng/mL (0–16). ^{68}Ga-DOTATOC-PET/CT (PET with gallium) showed a 6-cm multi-lobulated tumour-like mass in contact with the upper pole of the left kidney and the adrenal gland with SUVmax of 40.42. En bloc tumour resection with left kidney and adrenal gland was performed. Histological examination confirmed tumour recurrence consistent with a G2 pNET (Ki-67: 8%).

PTHrP-mediated hypercalcaemia in pNET is rare, with fewer than 50 cases reported, and tends to be associated with a poor prognosis. The average age at diagnosis is around 50 years (34–69), it affects males and females equally, lesions are usually detected on Octreoscan and gallium PET, and patients often have symptoms related to hypercalcaemia. A massive 95% are detected in stage IV, with liver metastases being the most common.[2–6] In terms of histology, more than 75% of cases were G1-G2, with a higher percentage of G2 in some series[2–6]; different lines of antitumour treatment (for example, somatostatin analogues, everolimus) were usually necessary to control the hypercalcaemia. Our case was also a young male, with symptoms related to hypercalcaemia, but, unusually, no metastases and good control after initial surgery, although he developed a recurrence eight years later. The recurrence also showed uptake on PET with gallium.

In terms of diagnosis, it should be noted that, in most published cases, the onset of symptomatic hypercalcaemia is usually several months or even years after the diagnosis of pNET. In our study, and in limited cases,[4] the disease was diagnosed based on the finding of hypercalcaemia. Other studies have reported cases in which hypercalcaemia appeared later.[3,4]

In our case, the patient first developed symptoms suggestive of hypercalcaemia and weight loss. The suppressed PTH value suggested a possible malignant origin, ruling out primary hyperparathyroidism. From the imaging tests, pNET was initially suspected, with increased NSE also supporting this diagnosis. It would also have been of interest to request CgA, not only for the initial diagnosis but also for monitoring after surgery, although it has been found that in some cases CgA can be normal.[6] We might also have ordered measurement of other pancreatic hormones such as gastrin, somatostatin, glucagon and pancreatic polypeptide, to determine whether there was hormone co-secretion, which has occurred in some cases.[4]

In terms of follow-up, imaging tests are recommended every three-to-six months for G1/G2 NET and every two-to-three months for G3 NET.[7] Follow-up should be lifelong, although frequency can be extended to every 1–2 years as time progresses.[7] Imaging for somatostatin receptors (Octreoscan/PET with gallium) is recommended at 12–36 months if over-expression was demonstrated by imaging in the primary tumour.[7] These guidelines were followed in our patient, and hypercalcaemia was detected by the blood tests, alerting to the possibility of recurrence. CgA is usually used, as well as NSE, the latter being particularly useful in G2 and G3 when CgA levels are normal.[7] In our case, however, both values were normal. There are currently no recommendations in cases similar to ours, due to their exceptional nature, but what should be emphasised is the importance of long-term follow-up in these patients, including serum calcium levels when ordering blood tests.

In conclusion, early diagnosis of pNET associated with PTHrP-mediated hypercalcaemia is important as they tend to be more aggressive. Therefore, when hypercalcaemia is detected, once the most common causes have been ruled out, a targeted study should be conducted, as early diagnosis can improve the prognosis for these patients. After surgery, long-term follow-up should be carried out, and serum calcium monitoring can be useful for early diagnosis of recurrence.

Ethical considerations

Informed consent was obtained from all individual participants included in the study.

Funding

No funding to declare.

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2530-0180/

Concern about hypoglycaemia is mainly nocturnal: An infodemiology study

La preocupación por la hipoglucemia es principalmente nocturna: un estudio de infodemiología

Dear Editor,

Hypoglycaemia is associated with long-term negative consequences in people with diabetes, such as an increase in glycaemic variability and a higher risk of mortality.[1] A hypoglycaemic episode can involve acute symptoms, such as irritability, shakiness, tachycardia and confusion, which can progress to loss of consciousness, seizure, coma or death.[1] Considering the unpleasant symptoms that can accompany hypoglycaemia and its potential short- and long-term risks, it can often lead to anxiety and fear in people with diabetes,[2,3] leading to a reduction in their quality of life.[2,4] Nocturnal hypoglycaemia is common in patients with diabetes, given that almost 50% of all episodes of severe hypoglycaemia occur during sleep.[5] Thus, nocturnal hypoglycaemia can affect sleep quality.[2,6]

Considering that people might tend to search the Internet about a topic whenever it comes to their minds or worries them, we thought that people with diabetes worldwide would probably search more often for ''hypoglycaemia'' at