Dear Editor,

We have closely read the article entitled “Pancreatic endocrine tumours or apudomas” (1) published in your journal in April of 2011. Zollinger-Ellison syndrome (ZES) is a rare entity that is found amongst the differential diagnosis of pancreatic endocrine tumours. We present two clinical cases of ZES recently diagnosed in our centre.

Case reports

Case report 1. This is a 50-year-old female with an 11-year history of epigastralgia and diarrhoea that only improved with proton pump inhibitors (PPIs) with a return of symptoms within days of suspending the medication. The patient was sent for gastroscopy which revealed duodenal erosions (*Helicobacter pylori* negative). A complete laboratory workup for diarrhoea was ordered, including gastrin levels, which were greater than 1,000 pg/ml (normal value: 0-90 pg/ml) with the patient off PPIs for 1 week. Remaining laboratory tests were normal. Given these results, gastric pH was tested, revealing a value of 1.9. The study was completed with an endoscopic ultrasound (EUS) which was normal. Somatostatin receptor scintigraphy revealed a pathological radiotracer deposit on the lesser curvature of the stomach (Fig. 1A).

Given the diagnosis of ZES, the patient underwent surgery, which found the tumour in the location indicated by scintigraphy and extirpated. The pathology study is reported as an ovoid nodule measuring 2 x 1 x 1 cm, well delimited, with a well differentiated neuroendocrine carcinoma with clear cell morphology that metastasises to 2 adenopathies contained in the specimen. Immunohistochemistry was positive for CK 8, CK 18, CK CAM 5.2, CD 56, chromogranin, synaptophysin, enolase and S-100 in the tumour cells with a Ki-67 proliferating index of 2 % (Fig. 1 B-D). Follow-up scintigraphy 6 months later is normal and the gastrin has descended to 256 pg/ml. The patient is asymptomatic without the need for PPIs.

Case report 2. This is a 50-year-old male diagnosed with gastroesophageal reflux disease that started several years ago with daily vomiting and retrosternal pyrosis. The patient was referred due to poor symptom control despite double-dose PPIs. Gastroscopy was performed, which revealed thickening of the gastric and duodenal folds and multiple duodenal erosions with histology studies that were not suggestive of malignancy. In addition, EUS revealed a marked increase in the thickness of the gastric folds due to the mucosa but with no evidence of a tumour. Given the suspected diagnosis of ZES, gastrin levels were requested, the result of which was 1,750 pg/ml after 72 hours of not taking a PPI (the patient could not tolerate not taking it for any longer). Subsequent intragastric pH testing revealed values of 2. A somatostatin receptor scintigraphy revealed a pathological radiotracer deposit in the second and third portions of the duodenum, compatible with gastrinoma (Fig. 1E). Blood testing was completely normal, including calcium levels. The patient was sent for surgery, which revealed a 5 mm tumour in the second portion of the duodenum and another peripancreatic tumour which intraoperative pathology revealed as gastrinoma invasion. Wedge resection of the duodenal tumour was carried out with lymphadenectomy of the territories of the liver hilum, peri-duodenal and peripancreatic territories. Histology of the surgical piece reported a neuroendocrine carcinoma measuring 4 x 3 x 3 mm, well differentiated and located in the submucosa with an insular patter together with a metastatic periduodenal lymph node, capsular rupture and extension of the carcinoma to the soft tissues. Immunohistochemistry revealed that the tumour

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was positive for CAM 5.2 cytokeratins, ENS, synaptophysin and chromogranin with a DI-67 proliferating index of 1% with 1 mitosis in 10 HPF. The surgical piece had clear margins and contained 4 additional lymph nodes, none of which were metastatic. Following surgery, gastrin levels dropped to 340 pg/ml with PPIs and the follow-up octreoscan revealed a small accumulation of radiotracer in the second and third portions of the duodenum. Given the persistence of the disease at 3 months after surgery, treatment was started with somatostatin analogues. The patient remains asymptomatic.

Discussion

Zollinger-Ellison syndrome is a disease caused by ectopic gastrin secretion by non-beta islet cells of the pancreas which results in gastrin hypersecretion and a resulting hypersecretion of gastric acid. It is an underdiagnosed and undervalued disease, especially in patients with peptic ulcer in whom symptoms are often controlled with PPIs. The majority of patients are diagnosed between 20 and 50 years of age. We should suspect it in cases of multiple gastroduodenal ulcers and/or symptoms of abdominal pain, malabsorption, steatorrhea and diarrhoea. The diagnosis is based on high gastrin levels (ruling out other secondary causes) and examinations such as gastroscopy, octreoscan and EUS. It is notable for elevated gastrin levels together with a pathological radiotracer deposit on octreoscan (2-5), which occurred in our 2 patients. In 20-35% of cases, it is associated with multiple MEN-1 endocrine neoplasms (1,6).

The treatment of choice in non-metastatic cases is surgery with intraoperative identification and resection of the tumour. This achieves cure rates of up to 50% (7,8). It is rare for the tumour to not be located intraoperatively (including in those with negative imaging studies). The use of the Whipple technique in these cases is controversial (7,8).

In cases of persistent or metastatic disease, patients can opt for treatments such as chemotherapy, radiation therapy or somatostatin analogue therapy (as occurred in one of our patients), though the benefits are limited and 10-year survival is 30%, compared to 83% at 15 years in patients with non-metastatic ZES (7,9,10). Gastric secretion may not return to its normal level due to remnant gastric parietal cells, so 40% of patients require PPI treatment after surgery.

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Fig. 1. A. Somatostatin receptor scintigraphy with pathological radiotracer uptake in the lesser curvature of the stomach. B. Lymph node metastasis of a well-differentiated neuroendocrine carcinoma. C. Figure “B” magnified, revealing homogeneous round cells with salt-and-pepper chromatin, characteristics of neuroendocrine carcinoma. D. Enolase-positive immunohistochemistry. E. Somatostatin receptor scintigraphy revealing pathological radiotracer uptake in the second and third portions of the duodenum at 4 and 24 hours after administration of the radiotracer.
References