Gastric endocrine tumors type I: treatment with long-acting somatostatin analogs

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Abstract

Gastric endocrine tumors associated with autoimmune chronic atrophic gastritis (gastric carcinoid type I) are almost exclusively benign lesions with little risk of deep invasion of the gastric parietal wall. For this reason, the role of octreotide in the treatment of these neoplastic lesions is controversial. Nine patients with more than five type I gastric endocrine tumors each <1 cm in size, without invasion of the muscularis propria and with Ki-67 index lower than 3%, were treated with long-acting somatostatin analogs for 12 months. After 6 months and again after 12 months, all the patients underwent upper gastrointestinal (GI) endoscopy with multiple biopsies. The plasma chromogranin A (CgA) levels and the gastrin levels in the serum were also determined. In all patients, the gastric neoplastic lesions disappeared after 12 months of somatostatin analog therapy. We also observed a significant reduction of CgA and gastrin levels at 6 and at 12 months of therapy as compared with the baseline values. We demonstrate that somatostatin analog treatment provokes the pathological regression of type I gastric carcinoids. This therapeutic approach should be considered as a valid option in selected patients with multiple type I gastric endocrine tumors.

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Introduction

Three subtypes of enterochromaffin-like cell (ECL-cell) tumors (carcinoids) have been recognized (Rindi et al. 1993): type I lesions (70–80% of the total) are associated with autoimmune chronic atrophic gastritis (CAG); type II lesions (5–8%) are associated with gastrinomas and they result in Zollinger–Ellison syndrome (ZES), most frequently where ZES is associated with multiple endocrine neoplasia type I; type III (15–20%) are sporadic lesions arising in otherwise normal gastric mucosa and there is no evidence of associated hypergastrinemia (Rindi et al. 1993).

Neoplastic changes in ECL-cells (types I and II) are often associated with an elevated concentration of gastrin in the serum (Rindi et al. 1993). In fact, gastrin exerts a trophic effect on ECL-cells, which leads to hyperplasia and, in some cases, to gastric endocrine tumors (Waldum et al. 1998, Leh y et al. 2000). In particular, type I tumors occur mostly in women and are rarely symptomatic (Borch et al. 2005). They are non-functioning tumors, typically found during upper GI endoscopy for dyspepsia or for anemia (Borch et al. 1985). Type I tumors frequently present themselves as multiple polyps, usually <1 cm in diameter, localized in the gastric fundus. They are almost exclusively benign lesions with little risk of deep invasion of the gastric parietal wall (Rindi et al. 1999). These tumors have a good prognosis, with a 5-year survival rate quoted at 96%, which does not differ from an age-matched normal population (Borch et al. 2005, Hosokawa et al. 2005).

The European Neuroendocrine Tumor Society (ENETS) Consensus Guidelines (Ruszniefski et al. 2006) have suggested that, in patients with type I ECLomas, annual surveillance is sufficient for patients with tumors <10 mm in diameter. Otherwise, when the tumors are larger, endoscopic resection is
recommended for up to six polyps not involving the muscularis propria. In the remaining patients, local surgical tumor resection should be performed. Antral resection to avoid repeated and chronic gastrin stimulation of ECL cells is effective in 80% of type I tumors (Ruszniewski et al. 2006).

Although type I gastric endocrine tumors are almost exclusively benign lesions with little risk of deep invasion of the gastric parietal wall (Rindi et al. 1999), the role of octreotide in the treatment of these neoplastic lesions is controversial (Burkitt & Pritchard 2006, Ruszniewski et al. 2006). For this reason, we evaluated the role of somatostatin analog treatment in type I gastric endocrine tumors.

Patients and methods

From January 2000 to December 2006, all patients admitted to our unit with gastric endocrine tumors underwent the following study protocol. A baseline visit was made in which personal data, past medical history, and symptoms were collected; blood fasting samples were taken to assess thyroid function, anti-thyroglobulin, anti-thyroidperoxidase and anti-gastric parietal cell antibodies (APCA), the serum gastrin levels, and the plasma levels of chromogranin A (CgA); upper GI endoscopy with multiple biopsies in the antrum, body, fundus, and visible lesions were performed. Pathological analysis were carried out in all the samples in order to classify the type of CAG and the degree of atrophy of the gastric mucosa according to the updated Sydney system classification (Dixon et al. 1996). Furthermore, we evaluated the degree of endocrine cells proliferation (linear, micronodular and adenomatoid hyperplasia, dysplasia) and the presence of endocrine tumors at immunohistochemistry through the evaluation of CgA positive cells (Solcia et al. 1988,1995). Whenever possible, the Ki67 level was measured and histological detection (Giemsa modified stain) of Helicobacter pylori (HP) infection was assessed.

All patients underwent endoscopic ultrasonography (US) and abdominal US to rule out the presence of infiltration of the muscular wall, local lymph node involvement, and distant metastases.

All patients who had an endocrine tumor of the stomach associated with CAG, more than five neoplastic lesions <1 cm in size localized in the gastric mucosa, absence of invasion of the muscularis propria and a Ki-67 index lower than 3% were included in the study.

The therapy protocol was based on the administration of long-acting somatostatin analogs (octreotide-LAR, Novartis, Basel, Switzerland) at a dose of 30 mg i.m. every 28 days for 12 months. After 6 months and again after 12 months, all the patients underwent upper GI endoscopy with multiple biopsies in the antrum, body, fundus, and the lesions. We also determined plasma CgA levels (reference value <17 U/l with DAKO CgA ELISA kit, Dako A/S, Copenhagen, Denmark) and gastrin levels in the serum (reference value 20–100 pg/ml with Immulite-2000 Gastrin assay from Diagnostic Products Corporation, Los Angeles, CA, USA).

Ethics

The study protocol was approved by the Senior Ethical Committee of the Department of Internal Medicine and Gastroenterology of the University of Bologna and was carried out according to the Helsinki Declaration of human studies. All patients had given their written informed consent to participate in the study.

Statistical analysis

The descriptive statistics used were mean, s.d., and frequencies. The data of CgA and gastrin were analyzed by the Wilcoxon test. P values of <0.05 were considered statistically significant. The analyses were carried out using the SPSS version 15.0 for Windows XP.

Results

Forty-six patients were evaluated and nine of them met the inclusion criteria. The epidemiological, endoscopic, and pathological features of these nine patients are shown in Table 1. Five patients (55.6%) were male and four (44.4%) were female; the mean age at the time of diagnosis was 64.4 years (range 38–85). Four patients (44.4%) had autoimmune CAG (atrophy of body and fundus with positive APCA), while the remaining five (55.6%) had a multifocal CAG (diffuse gastric atrophy with negative APCA). At upper GI endoscopy, we found that all the patients had more than 10 lesions – in four (44.4%) the lesions were in the gastric fundus, in one in the body, and in four (44.4%) both in the body and fundus (Fig. 1a).

The atrophy of the gastric mucosa was mild in three patients (33.3%), moderate in five (55.5%), and severe in one. In eight patients, HP infection was absent. The pathological and immunohistochemical evaluations demonstrated that, in all patients, there was a well-differentiated gastric endocrine tumor associated with CAG. The mean Ki67 index available in all the patients was 1.3% (range 0.2–2.8%). Table 2 shows the different macroscopic features (presence and
localization of the lesions) and pathological patterns (neoplasia, hyperplasia, or absence of lesions) seen at endoscopy during follow-up. In four out of nine patients (44.4%), regression of all gastric lesions after 6 months of somatostatin analog treatment was found. In the remaining five, a reduction of the number of the lesions was found (Fig. 1b). In all patients, the lesions disappeared after 12 months of somatostatin analog therapy (Fig. 1c). At pathological evaluation, in eight out of the nine patients (88.9%), we observed a regression from well-differentiated endocrine tumor to micronodular hyperplasia after 6 months of treatment. After 12 months, the endocrine cells were normal in four patients (44.4%), while a micronodular hyperplasia was found in four (44.4%) and a linear hyperplasia was found in one (11.1%).

The plasma CgA and serum gastrin levels before starting treatment (baseline), after 6 months, and again after 12 months are shown in Fig. 2. We observed a significant reduction of CgA and gastrin levels between baseline values (CgA: 65.2 ± 75.0 U/l; gastrin: 1041.8 ± 566.4 ng/ml) and after 6 months of therapy (CgA: 33.2 ± 44.2 U/l, \( P = 0.017 \); gastrin: 688.4 ± 416.2 ng/ml, \( P = 0.038 \)), and between baseline values and after 12 months of therapy (CgA: 29.3 ± 24.5 U/l, \( P = 0.028 \); gastrin: 358.1 ± 272.3 ng/ml, \( P = 0.008 \)).

None of the nine patients reported gallbladder stones or sludge after 6 and 12 months of somatostatin analog treatment. Otherwise, eight out of the nine patients reported meteorism for 2–3 days after the first injection of somatostatin analogs.

Discussion
The management of gastric endocrine tumors is largely dependent upon the subtype and size of the lesion. Type I gastric endocrine tumors, which are associated with CAG and hypergastrinemia, can be treated with various approaches. Hirschowitz et al. (1992) claimed that an antrectomy rather than a total gastrectomy may be the most appropriate treatment for gastric endocrine tumors associated with CAG. Antrectomy in three patients resulted in normalization of the serum gastrin

### Table 1
Epidemiological, endoscopic, and pathological features of the nine patients enrolled

<table>
<thead>
<tr>
<th>No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Type of gastritis</th>
<th>APCA</th>
<th>Site of gastric lesions</th>
<th>Grade of atrophy</th>
<th>HP</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>73</td>
<td>AB</td>
<td>Neg</td>
<td>Fundus</td>
<td>Mild</td>
<td>Neg</td>
</tr>
<tr>
<td>2</td>
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<td>80</td>
<td>A</td>
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<td>Fundus</td>
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<td>Neg</td>
</tr>
<tr>
<td>3</td>
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<td>44</td>
<td>AB</td>
<td>Neg</td>
<td>Fundus</td>
<td>Moderate</td>
<td>Neg</td>
</tr>
<tr>
<td>4</td>
<td>F</td>
<td>73</td>
<td>AB</td>
<td>Neg</td>
<td>Body and fundus</td>
<td>Moderate</td>
<td>Pos</td>
</tr>
<tr>
<td>5</td>
<td>F</td>
<td>53</td>
<td>A</td>
<td>Pos</td>
<td>Body and fundus</td>
<td>Severe</td>
<td>Neg</td>
</tr>
<tr>
<td>6</td>
<td>M</td>
<td>72</td>
<td>AB</td>
<td>Neg</td>
<td>Body</td>
<td>Moderate</td>
<td>Neg</td>
</tr>
<tr>
<td>7</td>
<td>M</td>
<td>86</td>
<td>AB</td>
<td>Neg</td>
<td>Body and fundus</td>
<td>Moderate</td>
<td>Neg</td>
</tr>
<tr>
<td>8</td>
<td>F</td>
<td>46</td>
<td>A</td>
<td>Pos</td>
<td>Fundus</td>
<td>Mild</td>
<td>Neg</td>
</tr>
<tr>
<td>9</td>
<td>F</td>
<td>53</td>
<td>A</td>
<td>Pos</td>
<td>Body and fundus</td>
<td>Mild</td>
<td>Neg</td>
</tr>
</tbody>
</table>

A, autoimmune chronic atrophic gastritis; AB, multifocal chronic atrophic gastritis; APCA, anti-gastric parietal cell antibody; HP, Helicobacter pylori.
levels and in the disappearance of carcinoids in 6–16 weeks, and a follow-up 21–30 months after antrectomy showed no carcinoids or ECL-cell hyperplasia. Thus, the authors concluded that multicentric ECLomas in patients with pernicious anemia and achlorhydria appeared to be gastrin-dependent and disappeared after the normalization of serum gastrin by an antrectomy. On the contrary, Ahlman et al. have suggested that a prospective treatment protocol for multiple gastric carcinoids with type A gastritis should be the endoscopic removal of less numerous, small lesions as a first-step therapy, followed by an antrectomy at recurrence, while larger lesions should be excised in combination with an antrectomy. Total gastrectomy should be reserved for rare cases of invasive tumors with lymph node metastases (Ahlman et al. 1994). More recently, some reports have suggested that a careful endoscopic follow-up without any treatment might represent a reasonable and safe option in selected patients (Rappel et al. 1995, Hori et al. 2000, Ruszniewski et al. 2006, Ravizza et al. 2007). In a recent study, Hosokawa et al. (2005) enrolled eight patients with multiple gastric endocrine tumors associated with type A gastritis in a follow-up program without surgical resection. These patients were free from the development or metastasis of carcinoids after a mean follow-up of 5.8 years in spite of their continuous hypergastrinemia, and the authors concluded that patients with multiple type I gastric endocrine tumors should not undergo surgical resection, but should instead be followed-up endoscopically. Finally, we found that gastric endocrine tumor regressed in three patients who had ZES and a family history of multiple type I endocrine neoplasia after long-term treatment with somatostatin analogs (Tomassetti et al. 2000). The regression of the tumors was related to the decrease in serum gastrin levels and the hypothetic antiproliferative effect of somatostatin analogs on ECL-cells in both animals and humans (D’Adda et al. 1996, Bakke et al. 2000, Tomassetti et al. 2000, Erlandsen et al. 2007).

In the present study, we evaluated the effect of this therapy on a selected group of patients aiming to better investigate the putative role of octreotide in type I gastric endocrine tumors. In particular, we chose patients with more than five lesions localized in the body and the fundus having a diameter <1 cm with pathological confirmation of well-differentiated endocrine tumor according to the WHO classification.

After 12 months of treatment with long-acting somatostatin analogs, complete regression of the neoplastic lesions in all patients was observed. The pathological examinations showed that, after 6 months, there was a regression from endocrine tumor to micronodular hyperplasia in eight patients (88.9%), while, after 12 months, the neoplasia disappeared in all the patients examined. These data are similar to those previously found by Fykse et al. (2004, 2005) in which

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Site of lesion at upper endoscopy</th>
<th>Pathological patterna</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Fundus</td>
<td>Endocrine tumors</td>
</tr>
<tr>
<td>2</td>
<td>Fundus</td>
<td>Endocrine tumors</td>
</tr>
<tr>
<td>3</td>
<td>Fundus</td>
<td>Endocrine tumors</td>
</tr>
<tr>
<td>4</td>
<td>Body and fundus</td>
<td>Endocrine tumors</td>
</tr>
<tr>
<td>5</td>
<td>Body and fundus</td>
<td>Endocrine tumors</td>
</tr>
<tr>
<td>6</td>
<td>Body</td>
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</tr>
<tr>
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<td>Body and fundus</td>
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</tr>
<tr>
<td>8</td>
<td>Fundus</td>
<td>Endocrine tumors</td>
</tr>
<tr>
<td>9</td>
<td>Body and fundus</td>
<td>Endocrine tumors</td>
</tr>
</tbody>
</table>

Table 2 Time course of the macroscopic features and pathological patterns seen at upper GI endoscopy

- aSolcia et al. (1988).
the author had treated five patients with one to five gastric endocrine tumors in CAG with octreotide-LAR 20 mg for 12 months. Moreover, we obtained the complete regression of endocrine tumors to simple hyperplasia in patients with higher number of lesions using octreotide-LAR 30 mg. Furthermore, there are some additional reports of the use of short-term octreotide therapy in patients with type I gastric endocrine tumors in which a reduction of endocrine cells in gastric mucosa after 3 months of treatment was described (Bordi et al. 1993, D’Adda et al. 1996).

We also found significantly lower CgA levels after 6 months and again after 12 months versus baseline plasma concentrations. This decrease could be due to both an inhibitory effect produced by somatostatin analog treatment on CgA secretion, and pathological changes from neoplasia to hyperplasia, as has already been reported by Peracchi et al. (2005). Finally, a statistically significant reduction in serum gastrin levels during SST analog treatment was also found. Other investigators have reported a similar decrease in serum gastrin levels after long-term treatment with octreotide in patients with ZES (Ruszniewski et al. 1988, Tomassetti et al. 2000) and in those with hypergastrinemic atrophic gastritis (Ferraro et al. 1996). Since hypergastrinemia plays an important role in the pathogenesis of gastric carcinoid tumors in patients with CAG, it is probable that the decrease in serum gastrin levels might have influenced the disappearance of the tumors.

In conclusion, we demonstrated that somatostatin analog treatment provokes the pathological regression of type I gastric endocrine tumors. This therapeutic approach should be considered as a valid option in patients with multiple type I gastric endocrine tumors <10 mm of diameter, without muscularis propria invasion or a high proliferation index. In our experience, medical treatment with long-acting somatostatin analogs can be used as a first line therapy and an alternative to follow-up (Ruszniewski et al. 2006, Ravizza et al. 2007). Further studies on a more consistent number of patients are necessary to confirm this initial observation and, most of all, to describe what happens in the long term after the end of treatment. In fact some authors reported a rebound of gastric endocrine cell after drug withdrawal without recurrence of gastric endocrine tumors (Bordi et al. 1993, Fykse et al. 2005).

In our experience, according to the ENETS guidelines, antrectomy still remains the treatment of choice in case of malignant development (deep invasion of the gastric wall) or recurrence despite local surgical resection or medical therapy (Ruszniewski et al. 2006).

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