Virchows Arch (1996) 428:237–241

ORIGINAL ARTICLE

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Pattern of gastric endocrine cells in microcarcinoidosis – an immunohistochemical study of 14 gastric biopsies

Received: 25 July 1995 / Accepted: 3 April 1996

Abstract A total of 14 gastric biopsy specimens from patients with microcarcinoidosis were analysed by immunohistochemical methods to evaluate the pattern of endocrine cell hyperplasia and dysplasia. All the patients had type A gastritis (autoimmune gastritis). Nonantral proliferations of gastric endocrine cells were classifed according to Solcia et al. All 14 cases had hyperplasia and 13 (92.9%) of them, dysplasia of gastric endocrine cells; 9 (64.3%) of the 14 were found to have showed a coexisting invasive gastric carcinoid at the time of diagnosis of microcarcinoidosis. The patients with invasive carcinoids had higher degrees and more complex forms of endocrine dysplasia (precarcinoid lesions). The average size of the foci of the microcarcinoidosis in gastric biopsies was 0.14±0.09 cm in the patients without invasive carcinoid, as against to 0.5±0.24 cm in the group of patients with associated invasive carcinoid. Microcarcinoid gastric biopsies about 0.5 cm in size, are suggestive of adjacent invasive carcinoid. However, even frankly invasive ECL carcinoids seem to be clinically less dangerous than was thought until recently.

Key words Gastric endocrine cells · Microcarcinoidosis · Immunohistochemistry

Introduction

Most gastric carcinoids occur in patients with autoimmune gastritis and pernicious anaemia or the Zollinger-Ellison syndrome; spontaneous carcinoid is very rare [12]. In autoimmune gastritis the advanced parietal cell atrophy first results in hyperplasia of the antral G cells with consequent hypergastrinaemia, which leads to proliferation of ECL (enterochromaffin-like) cells in the body of the stomach as a secondary effect [1, 5]. An histopathological classification for these nonantral endocrine cells was recently proposed by Solcia et al. [13], distinguishing hyperplasia, dysplasia (precarcinoid lesion) and neoplasia (see Fig. 1). The proliferations of gastric endocrine cells can also become manifest as gastric microcarcinoidosis [6], which is now defined as least one (often multiple) microcarcinoid(s) associated with precarcinoid (dysplastic) lesions. Solcia et al. [13] defined microcarcinoids as infiltrative or solid endocrine growths larger than 500 μm, confined to the mucosa and not visible macroscopically. Microcarcinoidosis is often discussed with regard to the risk of development of an invasive gastric carcinoid and the need for surgery. Our results suggest that the average size of microcarcinoidosis in gastric biopsies and both the degree and the combination of the complex endocrine proliferation pattern in endocrine dysplasia indicate the probability of coexistence of an invasive carcinoid.

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Materials and methods

Biopsy specimens from 14 patients were analysed. The specimens had an average size of 2–3 mm (range 2–8 mm). On average two samples taken from the body of the stomach with microcarcinoidosis (range 2–6 samples) were analysed by immunohistochemistry to disclose the gastric endocrine proliferation pattern, using the classification for nonantral proliferation of gastric endocrine cells proposed by Solcia et al. [13] (Fig. 1). After fixation in 5% buffered formalin and paraffin embedding, tissue sections were stained with haematoxylin-eosin and impregnated with silver according to Grimelius. In the other sections, immunohistochemistry was performed by the avidin–biotin method. Antisera were directed at chromogranin A (monoclonal mouse, Clone LK2H10 diluted 1:600, Boehringer Mannheim, Germany); chromogranin C (monoclonal mouse, Clone PHE 5, diluted 1:500–1000, Enzo); and somatostatin (polyclonal-rabbit, diluted 1:300, Dako, Glostrup, Denmark). In 4 cases antral biopsies were also available, and in these biopsies G cells were examined with an anti-gastrin antiserum (polyclonal-rabbit, undiluted, Biogenesis).

Results

Between 1986 and 1993, we diagnosed microcarcinoidosis in biopsies of the body of the stomach from 14 pa-

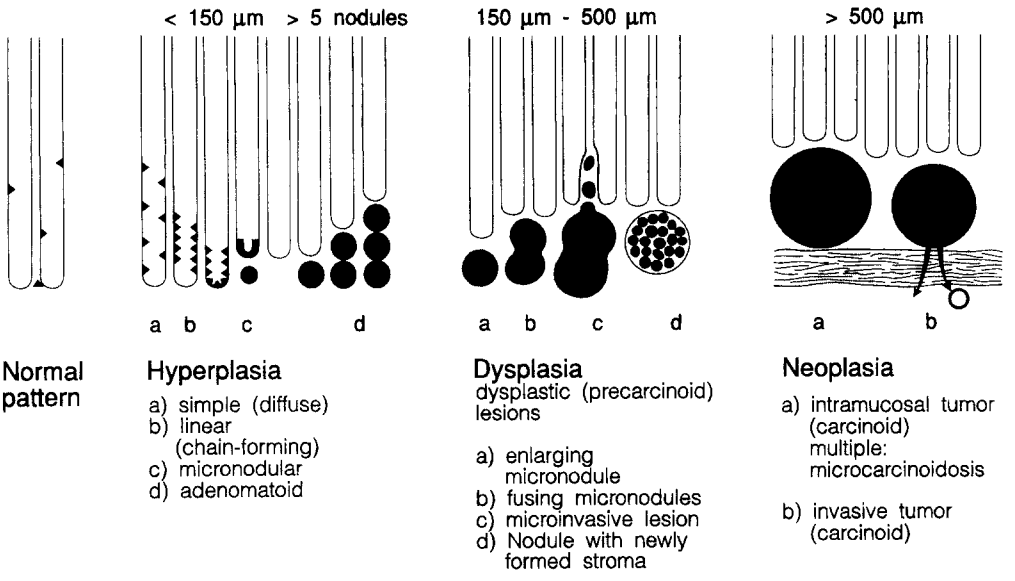


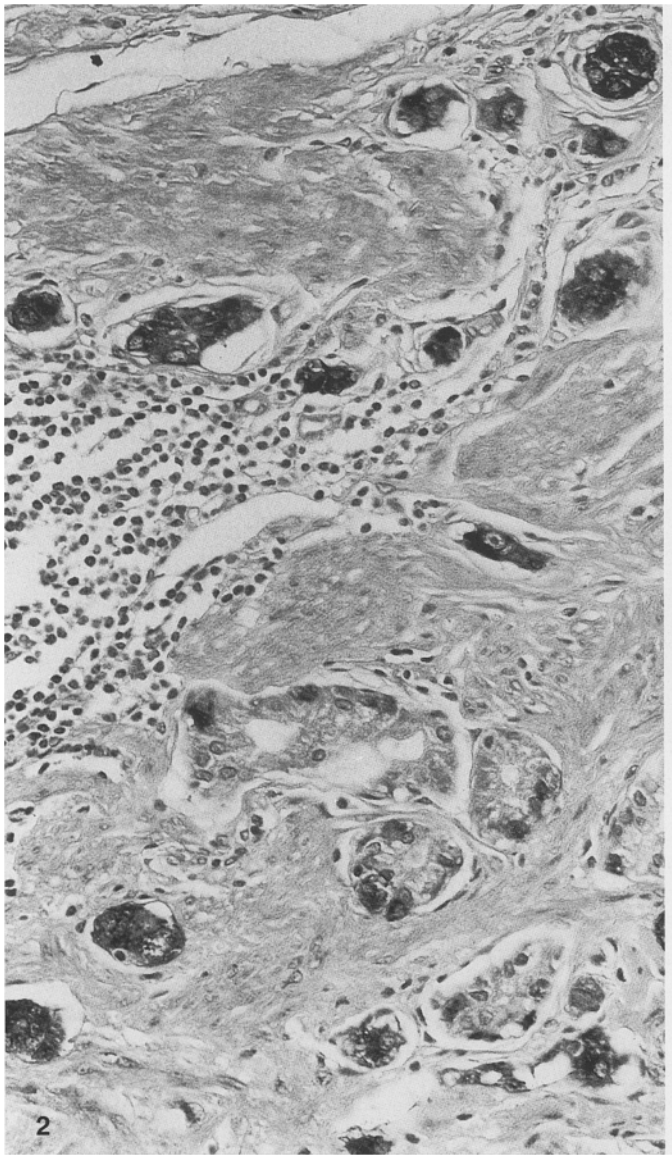
Fig. 1 Classification of nonantral gastric endocrine cells. (Deduced from [13])

Table 1 Distribution of nonantral gastric endocrine cells in corpus biopsies from 14 patients with (micro)carcinoids (*SM* submucosa, *M* muscularis propria)

Case no.	Hyperplasia				Dysplasia				Neoplasia	
	Diffuse	Linear	Micro-nodular	Adeno-matoid	Micronodules		Micro-invasive lesion	Nodule with newly formed stroma	Micro-carcinoid (size in cm)	Invasion (depth of infiltration)
					Enlarging	Fusing				
1	–	+	–	–	–	–	–	–	0.1	None
2	+	–	–	–	+	–	–	–	0.1	None
3	–	+	–	–	+	–	–	–	0.1	None
4	+	+	–	–	+	–	–	–	0.1	None
5	–	–	+	–	+	–	–	–	0.3	None
6	–	–	+	–	+	–	–	–	0.6	SM
7	–	+	+	+	+	–	–	–	0.4	SM
8	–	+	–	+	+	–	–	–	0.5	M
9	–	+	+	+	+	+	–	–	2×0.5	SM
10	+	+	+	+	+	+	–	–	0.3	SM
11	–	+	–	+	+	–	–	–	2×0.1	SM
12	–	+	–	+	+	–	+	–	0.5	M
13	–	+	+	+	+	–	–	+	0.3	SM
14	+	+	–	+	–	+	+	+	0.7	SM

tients. The mean age (±SD) of the patients was 60.6±21.3 years (range 37–88): 67.7±18.1 years for the 6 women and 64.1±10.0 years for the 8 men. Two patients were known to have pernicious anaemia and hypergastrinaemia, while no clinical data on such changes were available in the other 12 patients. In 6 (42.9%) of the 14 patients endoscopic examination showed polyps and in 4 of the 14 (28.6%), an erosion. Histologically, the biopsies of the gastric body showed atrophic gastritis in all patients, which was often severe. In 12 of the 14 biopsies one microcarcinoid each and in 2 out of the 14 cases two microcarcinoids each were observed (Table 1). The average size of the 14 microcarcinoid foci was 0.37±0.27 cm (range 0.1–0.7 cm). At the same time we demonstrated different types of hyperplasia and dysplasia of endocrine cells in the biopsies of the gastric body (Table 1) according to Solcia's classification of the nonantral proliferations of gastric endocrine cells [13]. The 14 patients were made up of 6 who had a micronodular and 8 who had an adenomatoid endocrine cell hyperplasia against a background of either simple or linear hyperplasia. In addition, there were dysplastic lesions in 12 of the 14 cases. There were 12 (85.7%) with enlarging micronodules, 3 (21.4%) with fusing micronodules and 2 (14.3%) with a microinvasive lesion or nodule with newly formed stroma.

There were often combinations of the different forms of hyperplasia and dysplasia of gastric endocrine cells, especially when the microcarcinoidal lesions were large. The 14 patients with microcarcinoidosis included 9 (64.3%) who had a coexistent invasive carcinoid in the gastric biopsy. The average size (0.5±0.24 cm) of microcarcinoids were clearly larger in the group of patients with an invasive carcinoid than in the group without invasive carcinoids (0.14±0.09 cm). Imunohistochemically, hyperplasia and dysplasia of the gastric endocrine cells



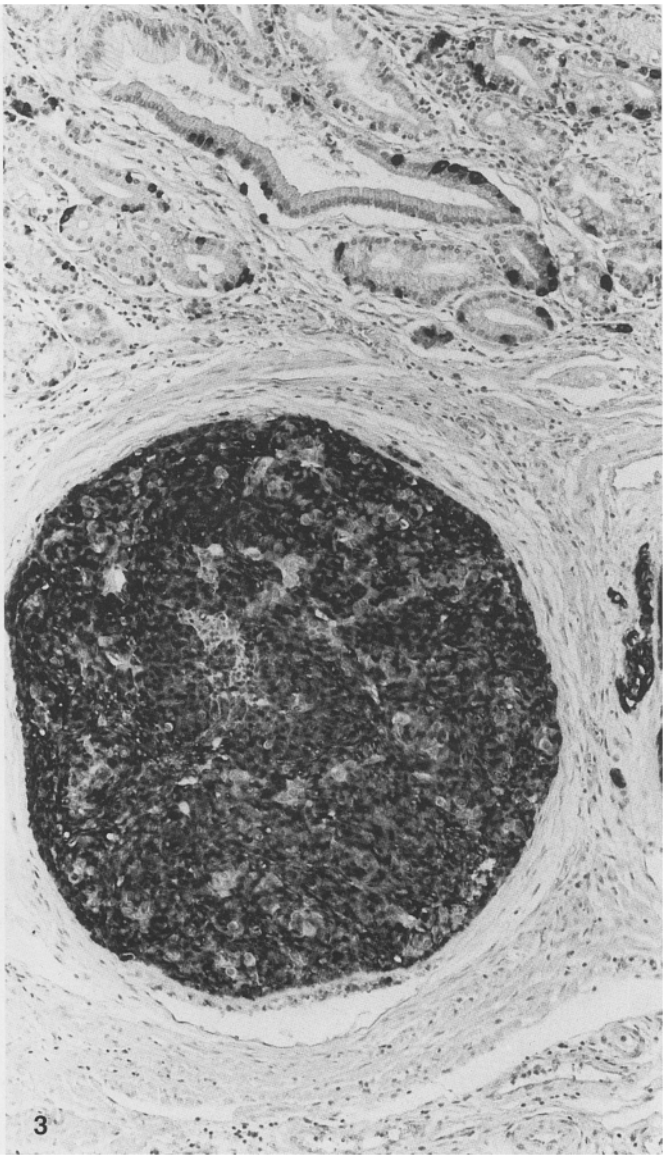


Fig. 2 Micronodular hyperplasia of gastric endocrine cells as revealed by immunostaining for chromogranin A. ×1200

Fig. 3 Example of a microcarcinoid; at the top mild linear hyperplasia in glands. Immunostaining for chromogranin A; ×400

and of the microcarcinoidal lesions showed a positive reaction with chromogranin A and C (Figs. 2–4). In no case was a positive reaction for somatostatin found. In addition, an argentophilic reaction was revealed by the Grimelius stain. Semiquantitative analysis disclosed only slight hyperplasia of gastrin cells in the 4 antral biopsies. No clinical data concerning hypergastrinaemia were available on these 4 patients.

Clinical follow-up

The clinical and endoscopic follow-up period ranged from 2 to 7 years, during which all 14 patients survived without clinical symptoms. No marked changes were observed in number, size or invasive pattern of the gastric endocrine cells during the follow-up.

In 2 of our 9 patients with invasive carcinoid in gastric biopsies an antrectomy was performed, while the others – partly because of their advanced age – were left untreated and underwent clinical and endoscopic monitoring only for more than 5 years.

Discussion

Microcarcinoidosis was first described in an autopsy case by Feyrter [6] using silver impregnation methods. The next case was in a patient with pernicious anaemia reported by Ratzenhofer [11]. With the advent of immunohistochemistry it became possible to visualize endocrine gastric cells and endocrine hyperplasia, dysplasia and microcarcinoidosis using antibodies specific for neuroendocrine proteins. Using such antibodies we had the

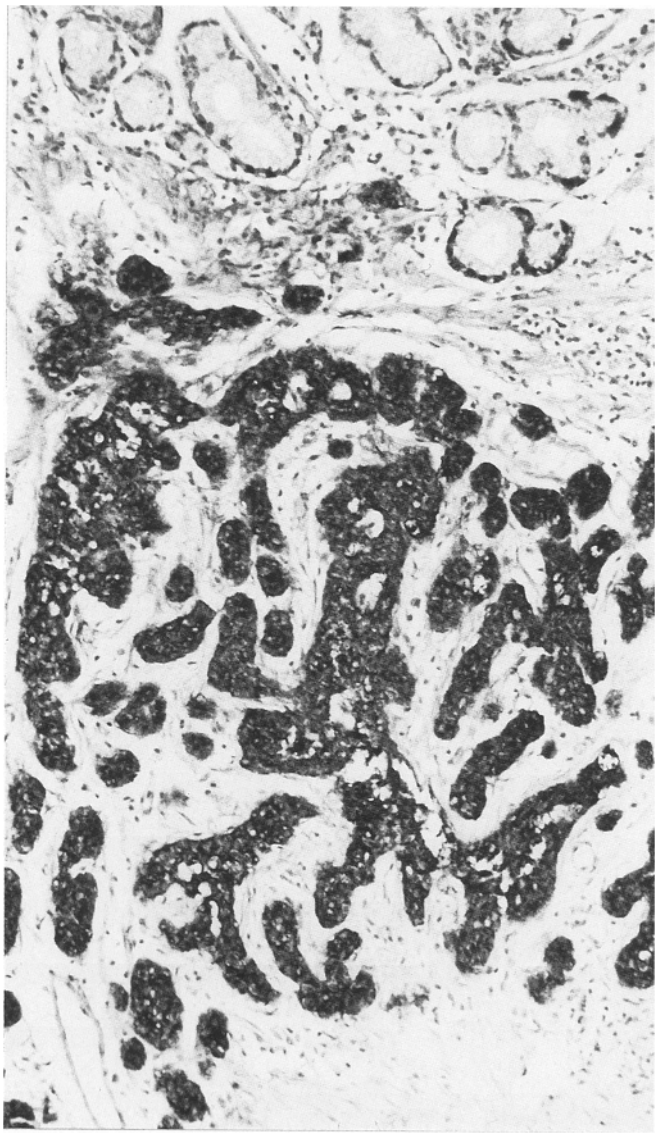


Fig. 4 Gastric invasive carcinoid, mainly trabecular. Immunostaining for chromogranin A; ×400

impression that the incidence and pattern of hyperplasia and dysplasia of gastric endocrine cells and the size of microcarcinoidosis indicated an association with invasive gastric carcinoid. In contrast to a previous report by Bordi et al. [1], 57.1% of our patients were male, and these showed an earlier manifestation (mean age: 64.1±10.0 years) than the female patients (mean age: 67.7±18.1 years); this may be due to the small number. All our patients suffered from type A gastritis. Although various combinations of the several forms of hyperplasia and dysplasia of gastric endocrine cells were observed, microcarcinoids more than 0.5 cm in size seem to be indicative of an accompanying invasive gastric carcinoid. We have to admit, however, that in individual cases it may be difficult to determine the maximum size of microcarcinoidal lesions in biopsy material, because in nearly 10% of all our small forceps biopsies parts of the submucosa were missing. Therefore, close cooperation between clinician and pathologist is important, since it is necessary to agree on an effective strategy for re-biopsy and adequate treatment. The distinction between intramucosal and invasive gastric carcinoids has no important consequences for the mode of treatment. Thus, a modified strategy of surgical intervention has been introduced for patients with gastric carcinoids, especially when these arise against a background of microcarcinoidosis. Antrectomy has been observed to be an effective surgical treatment [8], resulting in progressive reduction of the volume density, cross-sectional area and number of profiles of endocrine cells in the gastric cells in the gastric stump within a maximum of 10 months after surgery [4]. In other cases, spontaneous resolution of multifocal ECL cell gastric carcinoid tumours was observed in patients with pernicious anaemia [7]. This observation is confirmed by our study, which showed a clinically benign course for all patients during the 2- to 7-year period of endoscopic follow up without surgical intervention. According to the findings of Bordi [2] and Rindi [12], it is important to distinguish between multiple carcinoids occurring in patients with type A gastritis and sporadic carcinoids without type A gastritis. Carcinoids arising from microcarcinoids in conjunction with type A gastritis seem to have a better prognosis and lower tendency to metastasize than sporadic solitary carcinoids [3, 9, 10, 14].

In conclusion, our study shows that the proliferation pattern of gastric endocrine cells and the size of microcarcinoids may run in parallel with that of invasive carcinoid: both show hyperplasia and various kind of dysplasia, especially large micronodules, while other patterns of dysplasia seem to be more rare. However, these patterns of dysplasia and even neoplasia should not be regarded as an indication for therapy, as recent results have shown that ECL carcinoids of the stomach are relatively harmless, in contrast to sporadic carcinoids.

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