Risk of gastric carcinoma in patients with mucosal dysplasia associated with atrophic gastritis: a follow up study

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Abstract

Aims—To assess the risk of gastric carcinoma in patients with histologically verified dysplasia and atrophic gastritis of the stomach.

Methods—One hundred and one patients with mild (n = 84), moderate (n = 14), or severe (n = 3) dysplasia among 359 elderly men who smoked underwent gastroscopy because of low serum pepsinogen. Patients with dysplasia were prospectively followed up for an average of four years with repeated gastroscopies and multiple biopsies.

Results—Four of the 84 (4.8%) cases of mild dysplasia had progressed to moderate dysplasia during the follow up. Most of the cases of mild dysplasia had resolved spontaneously. No surgical intervention was required. Three of the 14 (21%) cases of moderate dysplasia had progressed to severe dysplasia, but no carcinomas were observed during follow up. Five moderately dysplastic lesions were removed surgically or endoscopically. In two of these five cases, moderate or severe dysplasia recurred. Two of the three severe dysplasias progressed to carcinoma.

Conclusions—In atrophic gastritis progression of mild and moderate dysplastic lesions seems to be a slow process and is rare in mild dysplasia. However, severe dysplasia is highly predictive of subsequent cancer. It is suggested that a five year follow up interval is sufficient in cases with mild dysplasia and two years in those with moderate dysplasia. Local removal of moderate dysplasia is indicated but does not guarantee that the lesion will not progress. Severe dysplasia requires immediate surgical intervention. (*J Clin Pathol* 1996;49:979-984)

Keywords: gastric dysplasia, gastric carcinoma, atrophic gastritis, follow up interval.

The overall prognosis of gastric cancer depends on the stage of the disease at the time of surgical treatment. The five year survival is favourable in the early stages (73-98%)¹⁻³; in resectable, more advanced disease it is only 38-43%.^{4,5} Gastric cancer seldom produces symptoms in the early stages and there are no reliable laboratory markers for screening.

Therefore, the only way to reduce the mortality in gastric cancer is to detect it early by rigorous follow up of patients at high risk.

Atrophic gastritis, gastric ulcer, pernicious anaemia, postgastrectomy stump and gastric polyps are risk factors for gastric cancer. Gastric dysplasia is regarded as a precancerous lesion and occurs more frequently in patients who have a risk condition than in those without. Gastric dysplasia is divided into three grades: mild, moderate, and severe according to criteria proposed by the expert committee of the World Health Organisation (WHO).⁶ The risk of cancer increases in parallel with the histological grade of dysplasia.^{7,8} Evidence suggests that severe dysplasia is highly predictive of gastric carcinoma.⁹⁻¹¹ On the other hand, mild dysplasia seems to progress to carcinoma only rarely.^{6,11,12}

Atrophic corpus gastritis is associated with increased or normal concentrations of serum pepsinogen II (PGII) but low serum pepsinogen I (PGI).¹³ A low PGI:PGII ratio is a good marker of atrophic corpus gastritis both in operated and unoperated stomachs.^{13,14}

We now report our follow up observations on 101 patients who had various degrees of dysplasia associated with atrophic corpus gastritis. The aim of the study was to evaluate whether dysplasia is a risk factor for gastric malignancy. The patients were collected from a series of 359 elderly men who smoked and who underwent gastroscopy because of low serum PGI concentrations and a decreased PGI:PGII ratio.

Methods

The series comprised 101 men with histologically verified dysplasia at the start of endoscopic follow up. They were screened from the participants of the Alpha-Tocopherol, Beta Carotene Cancer Prevention Study (ATBC Study), which was a randomised, double blind, placebo controlled primary prevention trial, to determine whether supplementation with α tocopherol, β carotene, or both, would reduce the incidence of lung and other cancers.¹⁵ The participants of the Study were male smokers aged between 50 and 69 years at entry, with blood samples at baseline and after three years of supplementation. Serum pepsinogen (PG) concentrations were measured in blood samples of 6297 men living in Helsinki and the surrounding Uusimaa Province, and those men

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with low pepsinogen concentrations (PGI < 25 ng/ml and PGI:PGII < 2.5) were invited for gastroscopy which was performed on 359 men after a supplementation of 3.9 years (median and range 3.7–5.6 years). Dysplasia of any grade was found in histological specimens from 101 men. The mean age of these patients was 63 years (range 51–73 years) at the time of gastroscopy. The participants were distributed among the four supplementation groups of the ATBC study as follows: α tocopherol 50 mg/day, 22 men; α -tocopherol 50 mg and β carotene 20 mg/day, 35 men; β carotene 20 mg/day, 21 men; and placebo, 23 men.

After dysplasia had been diagnosed at initial gastroscopy the patients were followed up with repeated endoscopies (mean three gastroscopies) for the mean time of 51 (range 22–70) months. Seven patients refused further endoscopies after the screening (initial) gastroscopy, and eight after the first follow up examination. It was technically impossible to perform gastroscopy in one patient. Three patients died before the first and one before the second control endoscopy for reasons other than gastric diseases. Eighty patients completed at least three endoscopies.

GASTROSCOPY AND GASTRIC BIOPSIES

The primary (initial) gastroscopy was performed between December 1989 and May 1992 by one of the authors (FL). The follow up endoscopies were performed by two of the other authors (AK and RH). The endoscopies were performed using an Olympus GIF XQ 20 endoscope. Routine biopsy specimens for microscopical analysis were taken at all endoscopies under visual control as follows: one biopsy specimen from the distal and one from the proximal antrum in the small curvature, and three biopsy specimens from the middle corpus in the greater curvature. The pH of the gastric fluid was also measured.

Multiple biopsy specimens from all endoscopically abnormal lesions (local colour change, ulcer, erosion, scar, abnormal fold, polypoid or tumorous lesions, etc.) were taken. Biopsy specimens were fixed overnight in neutral buffered 10% formalin, and embedded in paraffin wax. Histological sections were stained with haematoxylin and eosin, alcian blue (periodic acid Schiff 2.5), and modified Giemsa methods.

DIAGNOSIS OF MALIGNANCY AND DYSPLASIA

All histological samples were analysed by the same pathologist (PS). Gastritis and related histopathological appearances were noted and classified from antral and corpus biopsy specimens using the Sydney system.¹⁶ Dysplasia was diagnosed when epithelial atypia (cellular atypia) occurred in association with abnormalities in differentiation of the epithelium, and with abnormalities in the architecture of gastric foveolae and glands.^{6 7 17–19}

Dysplasia was initially graded into three categories: mild, moderate, or severe with further classification of the lesions into gastric (foveo-

Figure 1 Severe intestinal type dysplasia. (Haematoxylin and eosin.)

lar) or metaplastic (intestinal) types (figs 1–3).⁶ The mild category included cases in which the observed lesions were at most mild in degree, obscure, or indefinite—all cases with immature metaplasia (intestinal metaplasia types II or III)—were included in this category. Moderate or severe categories included all cases in which definite dysplasia was diagnosed—all lesions with adenoma-like growth patterns without evidence of malignancy (invasion)—were assigned to this category (moderate or severe dysplasia). Cases of “carcinoma in situ” type appearances were classified as severe dysplasia.

Carcinomas (tumours with definite invasion) were noted separately and were classified as diffuse, intestinal, and unclassified types according to the criteria of Lauren.²⁰

The concentrations of PGI and PGII in serum were determined by radioimmunoassay.²¹

Statistical analysis was performed using the Mann-Whitney U and Fisher’s exact tests; p values of < 0.05 were considered significant.

Results

PRIMARY ENDOSCOPY

Eighty four mild, 14 moderate, and three severe dysplastic lesions were found in the biopsy samples at primary gastroscopy from 101 of 359 patients who had low serum PGI and PGI:PGII ratios and were therefore endoscoped. At the initial endoscopy, four carcinomas were found. These patients were operated on and were excluded from the follow up study. The characteristics of the patients with dysplasia are shown in table 1.

Dysplasia was of intestinal type in 82 cases and foveolar type in 16 cases. Both types of dysplasia were seen in three patients. In 13

Figure 2 Moderate intestinal type dysplasia. (Haematoxylin and eosin.)

Figure 3 Mild gastric type dysplasia. Hyperchromatic atypical nuclei in highly regenerative glands can be seen, but there is no inflammation. (Haematoxylin and eosin.)

cases the dysplasia was found in polypoid lesions and in two cases in ulcerations. Pernicious anaemia was present in five patients. In 16 cases dysplastic lesions were found in gastric stumps (one lesion in the corpus mucosa and 15 lesions in the anastomosis).

Table 1 Patient characteristics

	Grade of dysplasia in primary gastroscopy		
	Mild	Moderate	Severe
N =	84	14	3
Age*	63 (4.9)	62 (6.6)	67 (7.4)
PGI* (ng/ml)	12.9 (6.2)	9.2 (4.0)	7.5 (4.9)
PGI:PGII ratio*	1.3 (0.6)	1.0 (0.4)	0.9 (0.4)
Gastric fluid pH*	6.4 (1.4)	6.2 (1.9)	7.0 (0)
Antrum atrophy:			
None	38	7	2
Mild	13	2	0
Moderate	6	2	0
Severe	13	1	1
Corpus atrophy:			
None	2	0	0
Mild	3	0	0
Moderate	39	5	0
Severe	40	9	3
Endoscopic appearances:			
Polypoid	6	7	0
Ulcerous	0	2	0
Colour change	12	2	1
Prominent fold	9	0	2
Random biopsy	57	3	0

*Mean (SD).

All severe and 78% (11 lesions) of the moderate dysplastic lesions were detected in visible lesions while 68% (57) of the mild dysplastic lesions were detected in random biopsy specimens. Moderate or severe dysplasia was found significantly more often in macroscopically visible lesions than mild dysplasia ($p = 0.0002$, Fisher's exact test) (table 1).

Intestinal metaplasia beyond the dysplastic lesions was found in 82 patients.

The dysplastic lesions were in the following sites: 48 antrum, 14 corpus, 19 angulus, 15 anastomosis, two pylorus, and three in both antrum and corpus. The atrophy in the antrum was graded as severe in 15, moderate in eight, and mild in 15 patients. The corpus atrophy was severe in 52, moderate in 44, and mild in three patients. Two patients had no atrophy (table 1).

The dysplasia was of foveolar type in 10 patients (63%) with previous partial gastrectomy and in nine (in three cases both types were present) patients without previous gastric surgery (11%) ($p < 0.0001$; Fisher's exact test). PGI values were significantly lower in patients with moderate or severe dysplasia than in patients with mild dysplasia ($p = 0.016$; Mann-Whitney U test). The PGI:PGII ratio was also lower in patients with moderate or severe dysplasia than in those with mild dysplasia ($p = 0.024$; Mann-Whitney U test). However, the pH values of the gastric juice did not show significant differences ($p = 0.881$; Mann-Whitney U test).

FOLLOW UP

During the follow up period from December 1989 to December 1995, two gastric carcinomas were found, both of which were "early cancers" (invasion limited to the submucosa). One gastric resection was performed due to moderate dysplasia. Additionally, two local excisions and one gastric resection were carried out because of severe dysplasia. Endoscopic polypectomies and/or laser treatment were

Figure 4 Evolution of mild dysplasia.

performed for seven lesions in six patients. No significant differences were observed between the different treatment groups regarding the evolution of dysplasia during follow up.

Mild dysplasia

The evolution of mild dysplasia is shown in fig 4. In this group no surgical or endoscopic treatments were performed. The mean follow up was 4.2 (range 1.8–5.6) years in those patients who had at least two follow up endoscopies (65 cases). No carcinomas were found during the follow up period. Progression to moderate dysplasia was observed in four patients (4.8%), two of whom had “regressed” back to mild dysplasia at the second follow up examination. In 36% of the patients mild dysplasia persisted at the first checkup examination, whereas in 62% the dysplastic changes were no longer found. At the second checkup

the corresponding figures were 40% and 59%, respectively

Moderate dysplasia

The progression of moderate dysplasia is shown in fig 5. No gastric carcinomas were observed in this group during follow up (mean time 4.2 years). In three of the 14 patients with moderate dysplasia at initial endoscopy (cases 2, 8, and 12) (fig 5), progression to severe dysplasia was observed. Two of these patients were operated on (local excisions) and no dysplasia was detected during the subsequent follow up period. The third patient who had severe dysplasia in the anastomosis was followed up endoscopically and the dysplasia was repeatedly considered moderate.

During the follow up period, four endoscopic polypectomies were performed on three patients for moderate dysplasia (cases 1, 2, and 10) (fig 5) in addition to one laser vaporisation and one partial gastrectomy (cases 5 and 14). In one patient (case 2) severe dysplasia was subsequently found in the upper corpus, while in the primary gastroscopy the dysplasia was found in the antrum. Local excision of this lesion was performed.

Among those on whom surgical or endoscopic interventions were performed, there was only one patient (case 5) with no dysplasia found at follow up. In all patients who did not undergo any procedures for dysplasia, the dysplasia was found at least once histologically.

Severe dysplasia

The progression of severe dysplasia is shown in fig 6. Severe dysplasia progressed to early carcinoma in two out of three patients. In one

Figure 5 Evolution of moderate dysplasia.

Figure 6 Evolution of severe dysplasia.

of these three patients the malignancy was detected six months after the primary gastroscopy, whereas in the other the malignancy was detected at the 34 month follow up. Endoscopic polypectomy and laser coagulation were performed on the third patient and no malignancy or dysplasia was detected in the endoscopy samples thereafter (26 months after polypectomy). The patient died 42 months after polypectomy from pneumonia and pulmonary abscesses without any evidence of gastric malignancy.

Discussion

Gastric dysplasia is generally regarded as a precancerous lesion. Correa²² proposed an aetiopathogenetic sequence from chronic gastritis to atrophic gastritis and to dysplasia, and, eventually, to gastric carcinoma. The Correa hypothesis is valid in the case of intestinal type gastric cancer and atrophic gastritis, while the diffuse type of cancer seems to be associated more often with non-atrophic gastritis.²³ Dysplastic lesions can often be found adjacent to gastric cancer, and it has been suggested by Japanese investigators that dysplasia and carcinoma are, therefore, simultaneous lesions, and that carcinoma can develop without preceding dysplasia.^{24 25}

In our study the two cancers were preceded by lesions which were classified into precancerous dysplasia, suggesting that the dysplasia-cancer sequence exists in the pathogenesis of gastric cancer in association with atrophic gastritis. There was also evidence that mild and moderate dysplastic lesions tended to progress into more severe forms. This progression also seems to occur along with worsening and progression of atrophic gastritis itself: an inverse association between the grade of dysplastic lesion and serum PGI was observed. Furthermore, patients with severe dysplasia were about five years older than the others.

This series comprises dysplastic lesions which were collected from a population of elderly smokers who were screened as a result of low serum PGI concentrations and a low PGI:PGII ratio, and who were subsequently subjected to endoscopy. The observations indi-

cate that a substantial proportion (28%, 101/359 men) of subjects with low serum PGI and PGI:PGII ratios have dysplastic lesions which may progress over time to gastric cancer, and this, therefore, suggests a need for follow up.

The risk of malignant transformation in patients with mild dysplasias varies between 0 to 11%, with follow up times varying from 18 to 42 months.^{11 12 26} In the present study no malignant transformation was observed during the mean follow up of 50 months in patients with mild dysplasia. The progression of these dysplastic lesions was rare, but does occur in some patients. Most (59%) of the mild dysplastic lesions “disappeared” during follow up. It may be that the risk of malignant transformation in patients with mild dysplasia associated with atrophic gastritis is similar to that reported in patients with atrophic gastritis in general (2.3–10.0%).^{27–30} Mild dysplasia is also a category of lesions where the real nature of dysplasia is indefinite. Pronounced regenerative proliferation or some immature forms of intestinal metaplasia that are included in this category do not seem to be particularly serious or dangerous lesions.

In patients with moderate dysplasia the risk of gastric malignancy varies from 2% to 35% during follow up periods of 13–42 months.^{12 26 31 32} In our study no gastric carcinomas were found in the group of 14 patients with moderate dysplasia. However, in three patients (21%) progression of dysplasia into the severe category was observed.

Severe dysplasia seems to be highly predictive of gastric malignancy, as reported before.^{9–11} Two out of our three patients developed definite gastric cancer. Both patients were operated on; the carcinoma was in its early stages and they are still alive and well at the time of writing. However, the time interval between the initial gastroscopy and cancer diagnosis was longer (six and 34 months) than previously reported. The third patient with severe dysplasia had his polyps removed and did not develop malignancy during the gastroscopic follow up period of 25 months.

Evolution of gastric cancer, even in defined precancerous lesions, seems to be very slow

according to our present experience. None of the subjects developed advanced cancer during the two to five years of follow up. In the two early cancer cases observed during the follow up the invasion was limited to the mucosa or submucosa at the time of surgery, suggesting that endoscopic surveillance is a safe policy for patients with dysplasia.

In two patients a pronounced (moderate and severe) dysplastic lesion was found during follow up at a site other than the initial lesion. This emphasises the multifocal nature of dysplasia in the atrophic stomach. The "disappearance" and "reappearance" of dysplastic lesions may also indicate their focal and patchy nature. Proper endoscopic diagnosis of dysplasia may, therefore, be complicated by sampling error. In spite of this difficulty, endoscopic follow up seems to ensure the detection of a malignant lesion early enough. A further noteworthy aspect is that most of the moderate or severe dysplastic changes occurred in visible lesions from which targeted biopsy specimens could be taken. None of the severe dysplastic and only three of the 14 moderate dysplastic lesions were found in biopsy specimens taken "randomly" from the stomach.

It has been emphasised before that most of the dysplastic lesions which progress to carcinoma are associated with ulcerations.^{2 9-11 32} In this study the association between gastric dysplasia and gastric ulcers was, however, rare. This may have been due to patient selection. The screening of atrophic gastritis was performed when PGI was low, a method which detects patients with atrophic corpus gastritis who, consequently, have hypo- or even achlorhydria. Therefore, ulcerous lesions are rare or absent.

The present series consists of patients with dysplasia associated with atrophic gastritis and warrants conclusions from this patient group only. We conclude that mild dysplasia in atrophic gastritis seldom progresses to carcinoma or even to moderate dysplasia. Therefore, we propose that in this category of dysplasia the endoscopic follow up interval could safely be set at five years. Moderate dysplasia is more problematic. It may progress relatively rapidly to severe dysplasia (as in three of 14 cases in this study) and may require follow up examinations more frequently. However, no cancers were found among these patients during follow up. We suggest that the follow up intervals could be two years in patients with moderate dysplasia. Local removal of dysplastic lesions may be indicated in this category, and after removal of the dysplastic lesion, the follow up interval could be lengthened. In contrast, severe dysplasia seems to be highly predictive of gastric malignancy and immediate surgery is indicated.

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