Gastritis and cirrhosis—no association

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SUMMARY Endoscopically sited gastric mucosal biopsies were taken from 98 patients with hepatic cirrhosis, and from 48 control patients. Nineteen patients with cirrhosis were found to have gastric ulcers, including eight with multiple erosions. In four of these eight, erosions were shown to arise in histologically normal mucosa. Among the remaining 79 patients with cirrhosis, the prevalence of chronic gastritis was not increased compared with controls of the same age-group. There was no increase in chronic gastritis in patients with alcoholic cirrhosis compared with either controls or patients with chronic active hepatitis and cirrhosis. The increased proneness of patients with cirrhosis to acute and chronic gastric mucosal lesions cannot be explained on the basis of an underlying chronic gastritis.

It has been suggested that patients with cirrhosis have an increased prevalence of chronic gastric ulcer,¹ and that they are particularly liable to haemorrhage from acute gastric mucosal erosions.² Because chronic gastric ulcers are invariably associated with some degree of chronic gastritis³ and since gastritis may also be a predisposing factor to erosions, we have studied gastric mucosal histology in patients with cirrhosis to assess whether their increased proneness to these gastric lesions is associated with an increased prevalence of underlying chronic gastritis.

Patients and methods

Gastric biopsies were taken prospectively from all patients with histologically-proven cirrhosis, who were undergoing upper gastrointestinal endoscopy in this unit. The series includes patients referred from other units because of the development of complications of cirrhosis. Two patients with previous gastric surgery were excluded. The series also excluded a few patients (less than 10) presenting with acute upper gastrointestinal haemorrhage whose condition did not allow prolongation of the endoscopy in order to take biopsies. The cause of cirrhosis in the 98 patients studied was: alcoholism 38; chronic active hepatitis 32; primary biliary cirrhosis 8; haemochromatosis 3; secondary biliary cirrhosis 1; and cryptogenic cirrhosis 16.

We examined a control series of 48 patients

endoscoped because of dyspepsia or weight loss. Thirty-six of the controls were ambulant outpatients, and none of the 12 inpatients was severely ill at the time of study. Controls were selected at endoscopy provided that no gastroduodenal ulcer, erosions, or carcinoma were found, and provided that there was no history of conditions associated with atrophic gastritis—for example, gastric ulcers, gastric surgery or pernicious anaemia.

Biopsy sites were identified endoscopically using fibre-optic instruments. For the first 48 patients with cirrhosis, biopsies were taken from three sites (1-3, Fig. 1), and in the subsequent 50 from four sites (1-4, Fig. 1). All four sites were biopsied in each of the control patients. 1-3 biopsies were taken at each site.

Biopsies were fixed in formol saline and sections stained with haematoxylin and eosin, and for

Fig. 1 Gastric biopsy sites.

reticulin. The histological classification was that of Whitehead, Truelove and Gear.⁴ In seven of the 98 patients with cirrhosis, only one gastric body mucosal biopsy was suitable for histological classification. In the 45 cases where biopsies from two sites were available and the 46 cases where biopsies from three sites were available, the histology at the different sites was the same in 83 of the 91 cases (91.2%). When gastric body biopsies at two or more sites were available, the one showing the most severe histological grade of gastritis was taken as representative.

Portal hypertension was deduced from the presence of oesophageal or gastric varices or both at endoscopy.

Serum was tested by indirect immunofluorescence for antibodies against gastric parietal cells (GPCA) and mitochondria (MA). All sera positive for MA at a dilution of 1/4 by immunofluorescence were titred using a liver mitochondrial complement fixation test. Since MA react not only with liver but also GPC, attempts were made to see if, in some cases, the MA was masking a true GPCA. Three methods were used; (a) dilution experiments, (b) absorption of MA-positive sera with liver mitochondrial antigen and (c) comparison of results obtained with unfixed as opposed to acetone-fixed tissue sections.⁵

Statistical analysis was performed using the χ^2 test.

Results

Nineteen patients had gastric ulcers. Eleven had one or two discrete ulcers (six antrum, five body) and eight had more than two lesions (four antrum, two body, two both body and antrum). Mucosal histology was similar in the two groups (Table 1) with the antrum more severely affected by gastritis than the body. In the four patients who had multiple erosive lesions of the body of the stomach, all of the biopsies from the body were histologically normal.

The remaining 79 cirrhosis patients had no gastric pathology evident at the time of endoscopy, nor any past history of lesions likely to be associated with gastritis. Their age and sex distribution is shown with that of the controls in Table 2. Their

histological findings are compared with the controls in Fig. 2. The prevalence of chronic gastritis increases

Fig. 2

Fig. 3

Fig. 2 Histological findings in control (Co) and cirrhosis (Ci) patients without gastric ulcer.

Fig. 3 Histological findings in alcoholic cirrhosis (Al) and chronic active hepatitis with cirrhosis in patients without gastric ulcer.

(Numbers at column head are subjects from whom adequate biopsies were obtained; p values show significance of differences in proportions of different histological findings between controls and cirrhosis patients: χ^2 test.)

Table 1 Mucosal histology in cirrhosis patients with gastric ulcers

	Mean age (yr) (and range)	Antral mucosa histology			Unsuitable	Body mucosa histology		
		Normal	SG	AG		Normal	SG	AG
One or two ulcers	59.2 (35-73)	1	4	4	2	4	3	4
More than two ulcers	54.2 (38-72)	2	1	4	1	5	1	2

SG = superficial gastritis.
AG = atrophic gastritis.

Table 2 Age distribution of control patients and cirrhosis patients without gastric ulcer

Age (yr)	Cirrhosis					Control	
	M	F	Alcoholic	CAH	Others	M	F
0-19	1	1	0	2	0	0	0
20-39	7	6	6	4	3	6	11
40-59	27	20	20	15	12	9	11
60+	9	8	5	4	8	5	6
Total	44	35	31	25	23	20	28

CAH = chronic active hepatitis.

with age in both controls and cirrhosis patients. The distribution of the histological grades in biopsies from either body or antrum does not differ significantly between cirrhosis patients or controls in any of the three age groups selected.

In the cirrhosis patients without gastric ulcer the prevalence of chronic gastritis in patients with alcoholic cirrhosis was not significantly different from that in patients with chronic active hepatitis and cirrhosis (Fig. 3).

In the cirrhosis patients without gastric ulcer there was no significant difference in the prevalence of chronic gastritis between men and women, or between smokers and non-smokers, or between patients with and without portal hypertension (Table 3).

In attempting to differentiate GPCA in the presence of MA, dilution experiments showed that in all cases when the MA level had been diluted out the serum was negative for GPCA. This is not surprising since in sera positive for GPCA alone, the antibody was present at a dilution of 1/10 but absent at a dilution of 1/20. Absorption was found to be practicable with low titred MA but not realistic with high titred sera and the acetone fixation technique could only be interpreted with difficulty.

The serological findings are shown in Table 4. Although immunofluorescence against GPC was more frequent in the patients with chronic active

Table 4 Serological findings

Diagnosis	No of patients studied	No with positive MA (Titre > 1/16)	No with true positive GPCA
Control	46	1	1
Alcoholic cirrhosis	23	2	1
Chronic active hepatitis and cirrhosis	24	10	2
Other cirrhosis	24	12	1

hepatitis that either the alcoholics or controls, in almost all cases the positivity could be attributed to cross-reactivity of the mitochondrial antibodies. The numbers of "true positive" GPC antibodies were small and there was no difference between the prevalence in controls and in either alcoholic cirrhosis or chronic active hepatitis with cirrhosis.

Discussion

Our finding that 19 out of 98 cirrhotic patients had gastric ulcers should not be taken as representing the prevalence of gastric ulcers in the general cirrhosis population, as our series was biased by the referral to us of patients with complications of their cirrhosis—for example, acute upper gastrointestinal bleeding.

Among the 19 patients with gastric ulceration were eight who had multiple minute lesions of the type referred to as gastric erosions. Although in the

Table 3 Influence of sex, smoking habit, and presence of portal hypertension on mucosal histology in cirrhosis patients without gastric ulcer

	No studied	Mean age (yr)	Antral histology (%)			Body histology (%)		
			Normal	SG	AG	Normal	SG	AG
Men	44	49.8	43	25	32	48	18	34
Women	35	48.5	39	15	45	51	9	40
*Smokers	45	49.6	41	27	32	49	20	31
Non-smokers	33	50.6	44	13	44	52	6	42
Varices present	57	49.3	40	20	40	49	12	39
†Absent	22	50.1	30	25	45	50	18	32

*Smoking habit not recorded in one case.

†Includes 3 patients studied after portosystemic shunts.

No significant differences (χ^2 test) in distribution of histological grades at either biopsy site.

SG = superficial gastritis.

AG = atrophic gastritis.

majority of these cases the antral mucosa showed gastritis, in five out of the eight cases the body mucosa was normal. Included among these five cases were all four patients in whom the multiple erosive lesions involved the body of the stomach. It is therefore clear that gastric erosions may develop in cirrhosis patients without preceding gastritis. None of these eight patients had taken either salicylates or alcohol for at least 72 h preceding endoscopy. While four were ill with ascites and encephalopathy, four, including three of the patients with erosions in the body of the stomach, came to endoscopy after small gastrointestinal bleeds which had not caused hypotension or encephalopathy. The pathogenesis of the erosions in these cases is unknown.

The importance attributable to our finding of a similar prevalence of chronic gastritis in the remaining 79 cirrhosis patients without gastric ulcers compared with control patients depends heavily on the validity of the control series. For ethical reasons the controls were not a normal population, but were selected from patients endoscoped because of dyspepsia or weight loss. Although all cases with lesions likely to be associated with gastritis were excluded, and although there is no clear evidence that chronic gastritis can cause dyspepsia, the selection of our control series might still have resulted in a higher prevalence of chronic gastritis than in a random population sample. However, comparison with published random samples^{6,7} suggests that our controls, in fact, have a similar or lower prevalence of chronic gastritis. Although the indications for endoscopy in the controls (dyspepsia 40; weight loss 8) were different from those in the cirrhosis patients (acute bleeding 7; dyspepsia 7; varices assessment 65), it seems unlikely that this would influence the prevalence of gastritis in the two groups. We therefore conclude that there is no increased prevalence of gastritis among patients with cirrhosis.

The number of patients in any age group with either alcoholic cirrhosis or chronic active hepatitis is small, apart from those in the 40-59 year group. Although there is a tendency for more chronic gastritis in patients with alcoholic cirrhosis in this age group, the difference is not statistically significant.

When the patients with alcoholic cirrhosis are compared with controls in the 40-59 year age group, there is no difference in the distribution of the histological findings (Antrum $\chi^2 = 5.30$, $df = 2$, $0.1 > p > 0.05$; Body $\chi^2 = 4.4$, $df = 2$, $p > 0.1$). This finding is similar to those of Cox⁸ and Wolff,⁹ but differs from those of Roberts¹⁰ who found an increased prevalence of gastritis in alcoholics compared to controls. This difference may be partly explained by the fact that Roberts' alcoholics and

controls were inadequately age-matched, his alcoholics being older (mean 34.1 yr, range 23-52) than his controls (range 18-41 yr). A second possible explanation of the difference may be that if, as Roberts suggests, chronic gastritis develops at an earlier age in heavy drinkers, the greater prevalence of chronic gastritis seen by Roberts in younger patients might not be apparent in older groups of patients such as ours (aged 40-59) or those of Wolff (aged 50+ yr), as the prevalence of gastritis in the older controls increases for reasons other than alcoholism. We have not studied sufficient patients in the 20-39 age-group to comment on this possibility. Our findings in relation to chronic gastritis and alcoholism are not relevant to the well-recognised acute gastritis which complicates alcohol administration.¹¹ Only three of our 94 patients for whom information was recorded had taken alcohol in the 24 h before endoscopy, and none of them had evidence of acute gastritis.

There are no previous reports of gastric histology in patients with chronic active hepatitis and cirrhosis. Although these patients are known to have an increased incidence of other autoimmune conditions, we could find no evidence of an increase in chronic gastritis either with or without GPC antibody.

Thus, we cannot find an increase in the prevalence of chronic gastritis in patients with cirrhosis of any aetiology, and we therefore conclude that their increased prevalence of acute and chronic gastric mucosal lesions cannot be explained on the basis of an underlying chronic gastritis.

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