Types of atrophic gastritis in patients with primary Sjögren's syndrome

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Abstract
Histological examination of the gastric mucosa was performed in 44 patients with primary Sjögren's syndrome with extraglandular symptoms (mean age 51.9, range 22–76). Biopsy specimens were taken from each of three separate regions: the antrum, the corpus, and the transitional zone between the antrum and the corpus. The incidence of chronic atrophic gastritis was considerably higher in patients with Sjögren's syndrome than in the controls. In the young patients with Sjögren's syndrome, atrophic lesions were more common both in the antrum and in the corpus than in the control group. In middle aged patients, however, only the antrum, and in the elderly only the corpus, was much more commonly affected than in the controls. All three types of chronic atrophic gastritis occurred in patients with Sjögren's syndrome. Decreased gastric acid secretion was associated mainly with atrophic gastritis of types A and AB, whereas hypergastrinaemia occurred almost exclusively in gastritis of type A.

Among the gastrointestinal manifestations of Sjögren's syndrome (SS), chronic atrophic gastritis (CAG) is the most common finding. In several investigations the incidence of CAG in patients with SS was more than 65%.1 2 In the earlier studies, however, only a small number of relatively old patients with SS were examined, and the gastric involvement was analysed in a mixed group of patients, including those with primary and secondary SS. Because only the corpus mucosa was studied the types of CAG were not determined.

In our study histological examination of the antrum and corpus mucosa was performed simultaneously in patients with primary SS. Gastric acid secretion and serum gastrin concentrations were also measured, and the type of CAG was determined.

Patients and methods
Forty four female patients with primary SS with extraglandular symptoms were studied because of abdominal complaints in 38 cases (epigastric pain in 15 and dyspepsia with or without nausea in 23), and for other reasons, such as anaemia, weight loss, or lack of appetite, in six cases. Twenty one of the 44 were taking non-steroidal anti-inflammatory drugs or corticosteroids, or both, regularly, and 14 were taking them only occasionally. The mean age of the patients was 51.9 years (range 22–76) and the mean duration of disease was 10.3 years (range 1–23). All patients met the criteria for primary SS. The Copenhagen criteria, with two modifications, were used for the diagnosis of keratoconjunctivitis sicca and xerostomia. These were as follows: the parotid gland flow rate stimulated with 2-0% citric acid solution was considered abnormal if ≤1.5 ml/10 min/gland, and parotid gland scintigraphy or sialography, or both, were performed.

An Olympus GIF XQ fibrescope was used for endoscopic examination of the stomach. Two to five mucosal biopsy specimens were taken from the antrum, the corpus, and the transitional zone between the antrum and the corpus for histological examination. The specimens were fixed in formaldehyde, embedded in paraffin, and stained with haematoxylin and eosin in accordance with a modified Zimmermann differential method.5 Depending on the severity of mucosal involvement, two forms of gastritis were distinguished histologically. These were as follows: (a) chronic superficial gastritis. In this form the chronic inflammatory cell infiltration affected the superficial layer of the deeper parts of the mucosa, or both, without gland atrophy; (b) chronic atrophic gastritis, which was further divided into chronic preatrophic gastritis characterised by moderate atrophy of the glands and severe atrophic gastritis with total gland atrophy.6 When the atrophic lesions were localised only to the corpus the CAG was classified as type A, only to the antrum as type B, and when both regions were affected as type AB.7

Gastric acid secretion was determined by the Kay test with pentagastrin stimulation.8 The results were expressed in terms of basal acid output and calculated maximum acid output. The normal ranges of basal acid output and calculated maximum acid output originated from the measurements and experience of the gastroenterological team in our department. Basal serum gastrin concentrations were measured by radioimmunoassay with Amersham RIA kits and were considered normal if <80 pg/ml.

Serum immunoglobulins and different immunological variables, such as rheumatoid factor, antinuclear antibodies, anti-SSA, anti-SSB, and anti-native DNA (anti-nDNA) antibodies, LE cell phenomenon, complement C3 concentration, and circulating immune complexes, were determined in all patients.

For the histological examination 104 female patients with a mean age of 53.0 years (range 24–83) served as controls. They had been
admitted because of abdominal complaints. Patients with ulcer disease, gastrointestinal tumour, or autoimmune connective tissue disease were excluded from the study. Functional diseases, such as irritable bowel syndrome and Oddi sphincter dysskinesia, were established as the final diagnoses in 46 control patients, and organic diseases, including gallstone disease, acute and chronic cholecystitis, cholangitis, pancreatitis, Oddi sphincter sclerosis, urinary tract infections, large bowel diverticulosis, arteriosclerosis, and spondylitis, in 58. Twelve patients from the control group were taking gastric irritants (corticosteroids or non-steroidal anti-inflammatory drugs) before the examination of the stomach.

STATISTICS

After a one way analysis of variance the multiple range test (least significant difference procedure) was applied for the statistical evaluation of the age of the patients, the duration of the disease, basal acid output, calculated maximum acid output, concentrations of serum gastrin, immunoglobulins, complement C3 concentrations, anti-nDNA, and haematological variables. The exact Fischer test and McNemar test were used for statistical analysis of the incidence of antinuclear antibodies, rheumatoid factor, LE cell phenomenon, SSB/SSA antibodies, and the histological findings on the gastric mucosa.

Results

Table 1 shows the histological results for the gastric mucosa. In patients with primary SS atrophic signs occurred more commonly in the antrum than in the corpus, but the difference was not statistically significant. The severity of atrophy was milder in the antrum than in the corpus, however. The occurrence of atrophic lesions was more than 1·5 times more common in patients with primary SS than in controls, both in the antrum and in the corpus, but the difference was significant only in the antrum (p=0·024).

The incidence of CAG depended on the age of the patients with SS (fig 1). In the young patients with SS atrophic mucosal lesions were two and a half times more common in the antrum, and four times more common in the corpus, than in the control group. The differences between the two groups were not significant (antrum: p=0·206, corpus: p=0·067), probably owing to the small number of young patients with SS. In the middle aged patients with SS only the antral atrophic lesions were significantly more common than in the controls (p=0·016). In contrast, in the elderly the corpus was affected more commonly in the patients with SS than in the controls, but the difference was not significant (p=0·22).

Table 2 shows the distribution of the types of CAG. In the 44 patients with SS gastritis of type A occurred in nine, gastritis of type B in 14, and gastritis of type AB in eight patients. In four cases the type could not be classified because the atrophic lesions occurred only in the transitional zone between the antrum and the corpus, and in the remaining nine cases the main regions of the stomach were not affected or showed characteristics of chronic superficial gastritis only. The age distribution was similar in all histological groups of patients with SS.

The duration of disease was significantly higher (p<0·05) only in patients with gastritis of type A (mean 13·2 years) compared with those with a normal mucosa and chronic superficial gastritis (mean 6·5 years).

Figures 2 and 3 show the basal acid output, calculated maximum acid output, and the serum gastrin concentrations in the different groups. The basal acid output was decreased in most of the patients with SS, but the output was significantly lower only in the gastritis group of type A compared with patients who had a normal mucosa or chronic superficial gastritis (p<0·05). The calculated maximum acid output was especially low in the gastritis groups of types A and AB, and compared with patients with a normal mucosa or chronic
Table 2 Types of chronic atrophic gastritis in 31 patients with primary Sjögren’s syndrome (SS) and in 44 controls (C). The number of patients affected is given.

<table>
<thead>
<tr>
<th>Age groups (years)</th>
<th>A (corpus)</th>
<th>B (antrum)</th>
<th>AB (corpus + antrum)</th>
</tr>
</thead>
<tbody>
<tr>
<td>SS</td>
<td>C</td>
<td>SS</td>
<td>C</td>
</tr>
<tr>
<td>&lt;44</td>
<td>3</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>45-59</td>
<td>3</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>≥60</td>
<td>3</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>Total (No (%))</td>
<td>9 (29)</td>
<td>14 (32)</td>
<td>14 (45)</td>
</tr>
</tbody>
</table>

Figure 2 Basal acid output (BAO) and calculated maximum acid output (cMAO) of gastric juice in patients with primary Sjögren’s syndrome. Gastric acid secretion was not measured in one patient. N/S = normal mucosa/chronic superficial gastritis; A = chronic atrophic gastritis of type A (corpus); B = chronic atrophic gastritis of type B (antrum); AB = chronic atrophic gastritis of type AB (antrum and corpus); T = chronic atrophic gastritis of transitional zone between antrum and corpus only.

Figure 3 Serum gastrin concentrations in patients with primary Sjögren’s syndrome. Concentrations were not measured in two patients. For abbreviations see fig 2 caption.

superficial gastritis the difference was significant (p<0.05).

Raised serum gastrin concentrations were found mainly in gastritis of type A, where the level was significantly higher than in the other histological groups (p<0.05).

The IgG concentrations were significantly higher in patients with gastritis of type A and in patients with atrophic gastritis only in the transitional zone of the stomach than in those without atrophic lesions (p<0.05). A mild anaemia and lymphocytosis occurred in each histological group, but most commonly in the group of type A. Significant differences were not found in other variables.

The incidences of the most important extra-glandular symptoms were similar in patients with SS with or without CAG: articular in eight, respiratory in four, vascular (skin vasculitis, purpura, and Raynaud’s phenomenon alone or in combination) in three, and renal in three of the nine patients with SS without CAG, and articular in 33, respiratory in 24, vascular in 13, and renal in 10 of the 35 patients with SS with CAG.

Discussion

Epidemiological studies have shown that CAG is common in the general population, its incidence varying between wide limits.11 Villako studied 124 female patients and found CAG in the antrum in 31% and in the corpus in 33%.12 In our control group the incidence of CAG was similar to these findings. The incidence of CAG varies in different ethnic groups, possibly owing to genetic factors and also environmental factors (eating habits, alcohol intake).13 14 It is generally accepted that the incidence of CAG increases with age.11 14 It occurred in about half of the subjects over the age of 50 described by Siurula.15 In our controls the incidence of atrophic lesions in both regions of the stomach was significantly higher in the elderly than in the young subjects (p<0.05). It is interesting that CAG may be present in about 30% of patients without abdominal complaints.9

The incidence of CAG in patients with SS has been reported to be extremely high. Buchanan found the presence of CAG in four of five patients with primary SS.1 Similar results were reported by Maury.2 Both groups studied only a small number of old patients, and only the corpus mucosa was evaluated histologically. Although the age of the patients with SS was lower in our study, the number of patients was higher and the duration of the disease was sufficiently long for it to serve as a suitable basis for an adequate evaluation of the incidence of CAG in primary SS. Chronic atrophic gastritis was found in the antrum and in the transitional zone between the antrum and the corpus in half of the patients with primary SS, and in the corpus in two fifths of the cases. It was found that the occurrence of CAG affecting either the antrum or the corpus was more common in young patients with SS than in the controls. In the middle aged patients with SS only the antral CAG was significantly more common than in controls, whereas for CAG in the corpus the two groups of patients did not differ. In contrast, in patients aged over 60 the corpus mucosa was more commonly affected in the patients with primary SS than in the controls. The latter findings are in agreement with those reported by Buchanan and Maury.1 2

Histological evaluation of the main regions of the stomach enabled us to determine the types of CAG in patients with primary SS. In such an autoimmune disease the AB type of CAG might have been expected to be the dominating form, but it was found that all three types of CAG occurred separately in primary SS, and in some cases only the transitional type showed atrophic lesions. Because the duration of disease was similar in all types of CAG (type A 13-2 years, B 11-0 years, AB 11-2 years) it is unlikely that type AB develops from gastritis of type A or B in the course of the disease.

It has been shown that types A and AB CAG are often associated with low HCl secretion or achlorhydria and with a low serum pepsigen concentration.15 In our patients with SS the basal acid outputs were decreased not only in type A and AB CAG, but often in patients with a normal mucosa or chronic superficial gastritis too. The calculated maximum acid output values, which characterise the functional capacity of the parietal cell mass, were significantly
diminished, however, only in atrophic gastritis of types A and AB. We did not measure the serum pepsinogen concentrations, but these were previously shown to be significantly lower in nine patients with primary SS than in patients with rheumatoid arthritis or systemic lupus erythematosus.17

It has also been reported that the serum gastrin concentrations are raised in patients with primary SS with CAG. In that study only the corpus was evaluated histologically.2 In our study raised serum gastrin concentrations occurred in all types of CAG, but the increase was most marked in gastritis of type A.

Interestingly, despite the common occurrence of CAG in patients with primary SS, true pernicious anaemia rarely develops in these patients.2 Only one of our patients with atrophic gastritis of type A showed a decreased absorption of vitamin B-12. The reason for this peculiar finding is not yet known but may be due to the fact that the CAG is patchy in most cases.

In the pathogenesis of CAG in primary SS the possible role of the often used antirheumatic drugs arises. Their essential role was not confirmed by Maury, as the incidence of CAG was only 35% in his control group, which comprised treated patients, mainly with rheumatoid arthritis.2 Kilpi verified, by immunohistochemical methods, that the composition of the mononuclear cell infiltration found in the gastric mucosa is similar to that of the salivary glands in patients with SS.18 In our study five of the patients with SS and six of 12 controls taking anti-inflammatory drugs showed no atrophic changes, whereas CAG was present in four patients with SS not treated with gastric irri-
tants. Although antirheumatic drugs were given to most of our patients with SS, we agree with Maury and Kilpi that the atrophic gastritis in SS is primarily caused by the underlying disease. A possible additional effect of anti-inflammatory drugs in the development of CAG cannot be completely ruled out, however.

To summarise our results, it may be concluded that the incidence of CAG in primary SS differs from that in the general population. Its occurrence varies with age in both groups, but whereas its incidence gradually increases with age in the normal population, in patients with primary SS the process occurs more commonly in the young, both in the antrum and in the corpus. In the antrum, a further increase can be detected in middle aged patients, followed by a decline in the elderly. In contrast, in the corpus the curve runs in the opposite direction and reaches its peak in old age. All three types of CAG may occur, but decreased gastric acid secretion is associated mainly with atrophic gastritis of types A and AB. Additionally, in gastritis of type A the serum gastrin concentrations are significantly raised.

16 Stockbrügger R. Chronic atrophic gastritis. Scand J Gastro-
enterol 1982; 17 (suppl 77): 72-6.