Gastroscopic screening in 80 patients with pernicious anaemia

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SUMMARY We have studied 80 patients with pernicious anaemia. Upper gastrointestinal endoscopy (with biopsy and cytology) showed no lesion other than atrophic gastritis in 34 patients. Thirty three patients, however, had varying degrees of gastric mucosal dysplasia, which was detected more frequently by histology than by cytology. The endoscopic appearance of the mucosa was abnormal in four of the six patients with moderate dysplasia, and in all three patients with severe dysplasia. One patient was found to have a small carcinoma in the gastric antrum, and underwent total gastrectomy; 18 patients had polyps (often multiple); four of these were treated by endoscopic polypectomy. One of the patients with polyps had multiple carcinoid tumours, and an asymptomatic parathyroid adenoma. Seventeen of the patients also underwent barium meal examination; abnormalities were revealed in only three of the seven patients with lesions visible at endoscopy. Our results justify further endoscopic studies in patients with pernicious anaemia, and sequential examinations to establish the natural history of gastric dysplasia.

Patients with pernicious anaemia are generally considered to have a risk of developing gastric carcinoma three to four times higher than that of control patients. The annual incidence of gastric carcinoma in patients with pernicious anaemia is around 1%. Gastroscopy (with biopsy and cytology) is the technique of choice for the diagnosis of carcinoma, which has an improved prognosis when detected at an early stage. There are few reports of endoscopy in patients with pernicious anaemia. Gastric carcinoma and polyps have been investigated but little attention has been paid to mucosal dysplasia, which might have important prognostic significance.

The present study was performed to assess the prevalence of benign, dysplastic and neoplastic lesions in a group of patients with pernicious anaemia, to compare the relative merits of histological and cytological methods for the detection of gastric mucosal lesions, and to explore the contribution of radiographic examination. The study was also designed to provide a cohort of patients with gastric dysplasia for long term follow-up.

Methods

PATIENTS Between July 1978 and May 1980, about 500 patients with a diagnosis of pernicious anaemia were traced through nine departments of general medicine, haematology, and gastroenterology in London. After reviewing the diagnostic criteria for pernicious anaemia, and after consulting the relevant specialists and general practitioners, 88 patients were invited for interview. They were accepted as suitable for screening if less than 70 years old (or fit and vital if older), and had no contra-indication to endoscopy (or to any surgery which might follow the discovery of a lesion). Eighty of these patients (44 men, 36 women) agreed to undergo endoscopy after being informed about its purpose, techniques, and risks. At the time of interview, their mean age was 61.8±1.5 SEM years, with a median age of 65 years. Twenty nine of the patients had some dyspeptic symptoms at the time of endoscopy.
Thirteen of the 80 patients underwent endoscopy at the time of diagnosis of pernicious anaemia. The mean duration of disease in all patients was $4.9 \pm 0.5$ years (range 0 to 21 years, median 4 years). The mean age at diagnosis of pernicious anaemia had been $56.7 \pm 1.6$ years (range 19 to 79 years, median 59 years). Half of the patients had had some neurological symptoms at presentation. The diagnosis of pernicious anaemia had been based on blood findings, bone marrow, gastric secretion tests, vitamin B12 and antibody estimations in 26 of the patients. In the remainder, a radio-isotope test of vitamin B12 absorption had also been performed. Only seven patients had had a gastric biopsy.

**BLOOD TEST**

Venous blood samples were taken for haemoglobin, ESR, iron, and iron binding capacity, biochemical screen, IgA, IgG, and IgM, gastric parietal cell antibodies, thyroid antibodies (Wellcome haemagglutination kit), intrinsic factor antibodies (radio-immunoassay, Dr G F Bottazzo, Department of Immunology, The Middlesex Hospital, London), gastrin (radio-immunoassay, Dr G Lundqvist, Akademiska sjukhuset, Uppsala, Sweden) and serum group I pepsinogen (radioimmunoassay, Dr H L Waldum, Regionsykehuset, Irdonheim, Norway).

**ENDOSCOPY**

Upper gastrointestinal endoscopy was performed on an out-patient basis by standard techniques, with Olympus P3 and Q instruments. All visible lesions were photographed. Brush cytology specimens were taken routinely from the antrum and gastric midbody, with two separate sheathed brushes; two to four slides were prepared from each brush, fixed in 74 OP Methanol, and stained by a modified Papanicolaou technique. Four biopsy specimens were then taken from the prepyloric antrum, and from the midbody in a crosswise manner (lesser curve, posterior wall, greater curve, anterior wall) and fixed in buffered formol saline. Specimens were processed routinely after orientation; a series of 5 μ sections were cut and stained with haematoxylin and eosin, combined PAS Diastase and Alcain Blue and by the modified Maxwell stain.11

Histological material was assessed independently by two pathologists, and classified by standard criteria.11

Mucosal dysplasia was defined according to the WHO working party on gastric carcinoma12 based on cellular atypia, abnormal differentiation, and disorganisation of normal glandular architecture, and graded as mild, moderate, or severe.

Additional brush and biopsy specimens were taken from all areas of endoscopic abnormality (polyps, areas of infiltration, ulceration, or acute congestion).

**RADIOLOGY**

Seventeen of the patients were referred for radiological examination by single contrast (n=3) or double contrast (n=14) techniques. All but one of the examinations were performed by one radiologist, who was informed about the diagnosis of pernicious anaemia, but not about symptoms or endoscopic findings.

**Results**

**INFLAMMATION AND ATROPHY OF GAstric MUCOSA**

*Antrum* Endoscopic findings suggesting inflammation (erythema, oedema, exudation, and erosion) were seen in the antrum in 36 of the 80 patients, but histological signs of inflammation were present in only 17 (mild 14, moderate three). There was no correlation between endoscopic and histological signs of inflammation. Atrophy of the antrum mucosa was diagnosed at endoscopy in seven patients, and in histology in six, but together in only one.

Mean serum gastrin was $789 \pm 82$ SEM pmol/l in the 62 patients tested. In five patients with atrophy and/or moderate inflammation of the antrum mucosa it was lower ($436 \pm 132$) than in the remaining 57 patients ($828 \pm 88$).

Intestinal metaplasia was found in the antral mucosa in 24 of the 80 patients. There was association with inflammation or atrophy in most, but in nine patients, intestinal metaplasia was present in otherwise normal antral mucosa.

*Body* Endoscopic signs of inflammation were seen in the body mucosa in 23 of the 80 patients, and visible atrophy in 68. Atrophic gastritis was found on histology in all 80 (moderate 47, severe 20, gastric atrophy 13). Intestinal metaplasia of varying degrees was found in 78 patients, in 59 of them together with pyloric metaplasia; pyloric metaplasia was seen alone in one instance. Mean serum group I pepsinogen was $38.5 \pm 4.0$ SEM ng/ml in the 63 patients tested; only in seven cases did the level exceed 70 ng/ml, the upper limit previously found in achlorhydria with this method. In these cases high values of serum gastrin corroborated the diagnosis of antrum sparing atrophic gastritis in all but one.

*Bile and dyspepsia* Gastric contents were bile stained in 32 of the patients; there was no correlation with histological inflammation or intestinal metaplasia of the gastric antral or body mucosa. There was, however, a correlation between the
Gastroscopic screening in 80 patients with pernicious anaemia

Gastroscopic screening with antral inflammation of had been reported contents.

CARCINOMA

Gastric carcinoma was diagnosed in a 53 year old woman with a four year history of pernicious anaemia. Her mother had had pernicious anaemia, and the patient herself was also being treated for rheumatoid arthritis and iron deficiency anaemia. She had no gastrointestinal symptoms, and a barium meal at the time of pernicious anaemia diagnosis had been normal. Endoscopy revealed a small area of infiltration 3 cm proximal to the pylorus, surrounding two ulcers, less than 7 mm in diameter; one of the ulcers had a small central blood clot. Biopsies from the lesion showed early gastric carcinoma (Fig. 1a,b); cytology was negative. Further biopsies taken at repeat endoscopy showed only moderate dysplasia in one of antral specimens. The antral mucosa was not inflamed, but showed marked intestinal metaplasia.

The patient underwent total gastrectomy. Histological examination of the specimen revealed moderate to severe dysplasia in most of the 82 sections examined (Fig. 2a,b), but no remaining focus of carcinoma.

DYSPLASIA

Mucosal dysplasia was found in 33 patients (24 mild, six moderate, three severe). Table 1 lists the most severe degree discovered by biopsy or cytology in either antrum or body. Dysplasia was evenly distributed between antrum and body mucosa, and in six patients was found in both areas. In four of the six patients with moderate dysplasia, and in all three with severe dysplasia, the changes were diagnosed by specimens taken from areas with visible lesions; however, visible lesions in five other patients revealed no specific histological or cytological abnormality. Histology was more sensitive than cytology in the diagnosis of dysplasia (Table 2). In 24 patients the diagnosis was made by histology alone; mild dysplasia was diagnosed by cytology alone in five patients. In one patient, cytology was suspicious of malignancy, but repeated histological examination showed severe and moderate dysplasia; the patient was finally listed as severe dysplasia. Correlation with clinical factors The mean age of the patients rises with increasing severity of dysplasia (Table 1) but only patients with moderate dysplasia had a slightly longer duration of pernicious anaemia than the other patients. There was no correlation between the presence of dysplasia and sex; family history of pernicious anaemia, autoimmune disease, and gastric carcinoma; dyspepsia; low body weight; abnormal blood tests; parietal cell,

Table 1 Gastric dysplasia in 80 pernicious anaemia patients

<table>
<thead>
<tr>
<th>Type of dysplasia</th>
<th>Antrum</th>
<th>Body</th>
<th>Both</th>
<th>Patients (no)</th>
<th>Mean age (yr)</th>
<th>Mean duration of pernicious anaemia (yr)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>16</td>
<td>13</td>
<td>5</td>
<td>24</td>
<td>62.5</td>
<td>4.4</td>
</tr>
<tr>
<td>Moderate</td>
<td>4</td>
<td>3</td>
<td>1</td>
<td>6</td>
<td>66.3</td>
<td>6.7</td>
</tr>
<tr>
<td>Severe</td>
<td>1</td>
<td>2</td>
<td>-</td>
<td>3</td>
<td>72.0</td>
<td>4.7</td>
</tr>
<tr>
<td>All</td>
<td>21</td>
<td>18</td>
<td>6</td>
<td>33</td>
<td>64.1</td>
<td>4.8</td>
</tr>
</tbody>
</table>

Fig. 1  (a) Intramucosal adenocarcinoma of the stomach. There is invasion of the lamina propria. H & E, ×25 (original magnification). (b) High power view showing invasion of lamina propria by irregular glands with back to back arrangement. H & E, ×100 (original magnification).
intrinsic factor, and thyroid antibodies; low levels of IgA and IgG; and mean levels of serum gastrin.

POLYPS
Gastric polyps were found at endoscopy in 18 patients (six solitary, 12 multiple – up to more than 50). Polyps were located in the antrum alone in six patients, in the body and fundus in 11, and in both areas in one. Polyps of the body and fundus were mostly multiple, whereas solitary polyps were more frequent in the antrum. Only five polyps were greater than 1 cm in diameter, the largest being 1-5 cm. Biopsies were taken from the base and surface of the polyps in 16 patients; most proved to be hyperplastic on histology (Table 3). Endoscopic polypectomy was performed in four patients with larger or macroscopically suspicious polyps. Histology of the removed polyps confirmed the previous biopsy diagnosis in three patients; in the fourth, the resected polyp showed a focus of severe dysplasia when previous biopsies had shown only hyperplasia and mild dysplasia. (Dysplastic polyps were not associated with any particular appearance.) The mean serum gastrin level of 15 patients with polyps was not different from the remainder.

One patient had multiple polyloid carcinoid tumours. She was an asymptomatic 51 year old woman with an eight year history of pernicious anaemia. Endoscopy showed at least 50 5–7 mm diameter sessile polyps in the gastric body and fundus (Fig. 3). Multiple biopsies from the polyps and from the surrounding tissue showed subepithelial proliferation of ovoid to polygonal cells (Fig. 4a,b). The cells stained with lead haematoxylin, and argentaffin granules were shown by a diazo technique. Electron microscopy revealed typical electron-dense neurosecretory granules, but immunohistological examination (Dr J Polak,

Table 2  Comparison of histology and cytology in 34 pernicious anaemia patients with gastric dysplasia and early gastric carcinoma

<table>
<thead>
<tr>
<th>Histology</th>
<th>0</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
<th>Carcinoma</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site: antrum</td>
<td>6</td>
<td>11</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>18</td>
</tr>
<tr>
<td>Number: single</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Number: multiple</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Site: body and fundus</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Site: both</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
<tr>
<td>Cytology</td>
<td>6</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>12</td>
</tr>
</tbody>
</table>

Table 3  Polypoid lesions in 80 patients with pernicious anaemia

<table>
<thead>
<tr>
<th>Patients with polyps at endoscopy (no)</th>
<th>18</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site: antrum</td>
<td>6</td>
</tr>
<tr>
<td>Number: single</td>
<td>6</td>
</tr>
<tr>
<td>Number: multiple</td>
<td>12</td>
</tr>
<tr>
<td>Site: body and fundus</td>
<td>11</td>
</tr>
<tr>
<td>Site: both</td>
<td>1</td>
</tr>
<tr>
<td>Site: body and fundus</td>
<td>12</td>
</tr>
<tr>
<td>Site: both</td>
<td>12</td>
</tr>
<tr>
<td>Cytology</td>
<td>18</td>
</tr>
<tr>
<td>Hyperplasia</td>
<td>8</td>
</tr>
<tr>
<td>Hyperplasia and severe dysplasia</td>
<td>1</td>
</tr>
<tr>
<td>Granulation tissue</td>
<td>1</td>
</tr>
<tr>
<td>Multiple carcinoid tumours</td>
<td>1</td>
</tr>
<tr>
<td>Mucosa with atrophy</td>
<td>1</td>
</tr>
<tr>
<td>Dysplasia (1), inflammation (1)</td>
<td>5</td>
</tr>
</tbody>
</table>
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Hammersmith Hospital, London) did not reveal their nature. Asymptomatic hypercalcaemia in this patient led to the discovery and subsequent removal of a parathyroid adenoma.

Intra-mucosal carcinoid cell hyperplasia was found on biopsies in one other patient without endoscopically visible lesions.

Comparison of radiograph and endoscopy findings

Seventeen patients underwent barium meal examination at the beginning of the study. Seven of these had surface abnormalities at endoscopy (infiltration, stiff folds, polyps, or erosions) which might have been detectable by barium meal; however, abnormalities were seen in only three: two patients with infiltrated mucosa due to moderate and severe dysplasia, and the patient with multiple APUD cell tumours, in whom the double contrast barium study revealed only the largest of the many polyps. Radiology did not reveal any lesion not previously diagnosed at endoscopy.

Discussion

The patients studied were not representative of pernicious anaemia patients in general; the method of selection meant that they were younger than average, and that the duration of pernicious anaemia was relatively short. For the same reason, however, they were well motivated and relatively healthy, and therefore representative of an appropriate group for screening.

The study provides further information about the gastric lesion in pernicious anaemia. Antrum sparing atrophic gastritis, as originally described, has been associated with a high serum gastrin level and antral gastrin cell hyperplasia, and designated as ‘atrophic gastritis type A’. However, 10–20% of patients with pernicious anaemia also have atrophic gastritis of the antrum, with gastrin cell reduction and normal serum gastrin levels. Antral atrophic gastritis was found in 7.6% of our patients; their serum gastrin levels were not impressively lowered indicating only a moderate degree of mucosal atrophy. The presence or absence of antral gastritis appears to have little clinical relevance. It could not be recognised endoscopically, and there was no correlation with the presence of bile in

Fig. 3 Multiple polypoid lesions of the body mucosa at the greater curve.

Fig. 4 (a) Carcinoid tumour of the stomach showing extensive infiltration of the lamina propria by polygonal cells. H & E, x10 (original magnification). (b) High power view showing an organoid pattern typical of endocrine tumour. H & E, x63 (original magnification).
gastric juice, or with dyspepsia. It is possible that the lack of acid in pernicious anaemia minimises the damage caused by duodeno-gastric reflux.

The main purpose of this study was to seek neoplastic and dysplastic lesions which might be expected in damaged mucosa. The yield was remarkably high. One patient had a small gastric cancer, 18 had polyps, and no fewer than 33 (41%) showed some degree of mucosal dysplasia. This was graded as mild in 24 patients (30%); mild dysplasia is particularly subject to observer variation and controversy, and is of dubious clinical significance. Dysplasia was graded as moderate, however, in six patients (7.5%), and severe in three (3.5%). These results are almost identical to those of a recent Swedish endoscopic study, also of 80 patients; one had cancer, 35 had polyps and eight showed moderate or severe dysplasia.

Histology was more sensitive than cytology in the detection of dysplasia in our study – probably because dysplastic changes were found mainly in the middle or deepest parts of the lamina propria; only in a few cases did cytology add to the diagnosis made from multiple biopsies. Dysplasia was evenly distributed between antrum and body; surprisingly, it was found in normal antral mucosa in eight patients, who did not differ from the remainder with respect to any local or general factor. This emphasises the likely importance of generalised intra-luminal factors, such as the increased formation of nitroamines from nitrites in achlorhydria because of bacterial overgrowth as shown by ourselves and others.

Most gastric polyps are hyperplastic, with little or no malignant potential. Two of our patients with polyps, however, had important histological findings (severe dysplasia, carcinoid tumour) and another study has shown that most of the dysplasia in pernicious anaemia is associated with polyps. We therefore recommend careful histological sampling of all polyoid lesions. Biopsy alone does not always provide representative material in patients with polyps; these should therefore be removed by snare diathermy for accurate diagnosis. The association of carcinoid tumours and carcinoid cell hyperplasia with pernicious anaemia is increasingly recognised.

Most patients with pernicious anaemia do not have severe dysplasia, and do not develop carcinoma. It would therefore be valuable to discover any predisposing factor or marker of highest risk. Unfortunately, we could identify no such link with any of the clinical, biochemical, or immunological data. We emphasise, however, that dysplasia is usually associated with visible lesions, and that multiple biopsies should be taken from any abnormal looking area. The double contrast barium meal can detect small lesions, but the results were not impressive early in this study. We abandoned radiographic examination because of the results, and the inconvenience for patients attending two examinations.

The yield of neoplastic lesions found by endoscopy in this and the Swedish study is higher than that in general screening programmes in countries such as Japan. That fact alone does not justify the widespread introduction of endoscopic surveillance for patients with pernicious anaemia. The discovery of a small cancer and of severe dysplasia poses difficult questions about clinical management; total gastrectomy is a major undertaking, especially for patients beyond middle age. The evolution of these lesions is not yet documented. It is evident that the value of regular endoscopic surveillance rests on the importance of mucosal dysplasia. Mucosal dysplasia is an important marker for the development of malignancy in the operated stomach and in longstanding colitis. Our own study and others are providing cohorts of patients with dysplasia for long term follow-up, in order to assess the risk, and the value of detection.

The results of this and the similar Swedish study certainly justify further assessment of endoscopic surveillance in patients with pernicious anaemia, a well defined high risk group for gastric cancer. We suggest that all patients with pernicious anaemia (except the most elderly and frail) should undergo endoscopy with multiple biopsies at least once at the time of diagnosis. The need for further surveillance will be determined by the initial findings, the clinical picture, and the results of current continuing studies.

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