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High incidence of upper gastrointestinal tract involvement in Crohn's disease

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Abstract A better definition of gastric mucosal histology in Crohn's disease permits a more accurate estimation of the frequency of upper gastrointestinal tract involvement in Crohn's disease. In a retrospective study of 792 patients with known Crohn's disease the incidence of lesions associated with the disease was determined in the duodenum, duodenal bulb, and gastric antrum and body mucosa. Crohn's disease was identified histologically in the antrum in 41.5%, in the body in 37.1%, in the duodenum in 12.1%, and in the duodenal bulb in 13%. In a further 15% and 17.4% of cases, Crohn's disease of the duodenum and duodenal bulb, respectively, was suspected. The positive predictive value of focal gastritis in patients undergoing upper endoscopy and not yet known to have Crohn's disease is as high as 94%. Thus, a high proportion of Crohn's disease patients show upper gastrointestinal tract involvement, with the major involvement in the antrum. Focal gastritis suggesting Crohn's disease turned out to have a high positive predictive value in patients not known to have Crohn's disease at the time of gastroscopy.

Key words Stomach · Duodenum · Crohn's disease · Focal gastritis

Introduction

It is well known that Crohn's disease can affect all sections of the gastrointestinal tract from the oral cavity to the anus. While the lower gastrointestinal tract has been well studied in patients with Crohn's disease, the upper gastrointestinal tract has attracted less attention. In gas-

tric resection specimens transmural inflammation hints towards Crohn's disease. The interpretation of gastric mucosal biopsy specimens, however, is usually difficult. The first studies addressing the issue of upper gastrointestinal tract involvement through endoscopy with biopsy found a low incidence (1–5%) of lesions in duodenal and gastric mucosa [5, 11]. Later, these results were challenged by studies reporting upper gastrointestinal tract involvement in 30–50% of the patients [1, 2, 4, 7, 8, 10, 13, 14], the majority of lesions being found in the stomach. The major shortcoming of most of these later studies [1, 2, 4, 7, 8, 10, 13, 14], however, was the unawareness of *Helicobacter pylori*, which is itself a major cause of gastritis [16]. Despite this shortcoming it has become evident that a particular type of gastritis, namely focal gastritis, is frequently observed in patients with Crohn's disease.

The identification of *H. pylori* as a major gastric pathogen led to an increased awareness of the different types of gastritis and finally to a more refined classification of gastritis. In the light of this new classification two studies [6, 12] have confirmed that focal gastritis is not associated with *H. pylori* infection but is indeed a feature of Crohn's disease.

The histology of gastric and duodenal Crohn's disease is now well defined and allows a more accurate estimation of upper gastrointestinal tract involvement. The aim of this study was therefore to determine the incidence of Crohn's disease of the upper gastrointestinal tract in 792 patients with known Crohn's disease, in the light of the new criteria. This is the largest series analysed so far and includes 82 patients who were not known to have Crohn's disease at the time of gastroscopy, enabling us to determine the positive predictive values of focal gastritis in the diagnosis of Crohn's disease.

Patients and methods

All patients who had undergone upper and lower gastrointestinal endoscopy with biopsy and for whom, in at least in one report, Crohn's disease was mentioned as either diagnosed or suspected,

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were retrieved from the files of 4 consecutive years of the Institute of Pathology in Bayreuth. Some 792 patients met the criteria. The median age of the patients was 31 years (range 2–87 years). Some 466 patients were female (58.3%), and 326 (41.2%) were male.

Biopsies were fixed in 10% buffered formalin and embedded in paraffin. At least eight semiserial sections were stained with haematoxylin and eosin. For visualization of *H. pylori* gastric biopsy specimens were also stained by the Warthin-Starry silver impregnation method.

In 82 cases (10.2%) gastroscopy was performed at least 1 year before ileocolonoscopy. In the remainder, gastroscopy and ileocolonoscopy were part of a diagnostic work-up and were performed in immediate succession (561 patients, 70.8%), or colonoscopy was performed at least 1 year before gastroscopy (119 subjects, 15%).

The diagnosis of Crohn's disease was based on the finding of characteristic radiological, endoscopic, and microscopic features elsewhere in the gastrointestinal tract and at clinical follow-up [9]. Histologically, Crohn's disease of the stomach was suspected when either discontinuous or focal inflammation with or without epithelioid granulomas was observed. Discontinuous inflammation was characterized by inflamed areas bordering directly on noninflamed mucosa. Focal inflammation was characterized by focal infiltration of the gastric pits or glands or, rarely, foveolae by mono- and polymorphonuclear leucocytes (Fig. 1). In the latter, the inflammatory infiltrate was found around either one or a few (usually fewer than ten) glands. In patients with *H. pylori* colonization Crohn's disease of the stomach was only considered in cases with epithelioid granulomas. Crohn's disease of the duodenum and duodenal bulb was diagnosed according to standard criteria [15] (Fig. 2).

Results

Crohn's disease of the duodenum was found in 43 (12.1%) patients. Histology revealed the occurrence of granulomas in 33 of these cases. In 53 (15%) patients Crohn's disease was suspected but could not be definitely diagnosed. Finally, in 27 (7.6%) patients duodenitis was found, which remained unclassified with respect to its aetiology. In 231 (65.3%) subjects the duodenal mucosa was considered normal.

Crohn's disease was found in the duodenal bulb in 73 (13%) patients, including 22 with granulomas. In 98 (17.4%) patients Crohn's disease was suspected but could not be definitely diagnosed. In 23 (4%) patients bulbitis remained unclassified with respect to its aetiology. In 294 (52.3%) subjects a normal mucosa was found.

Focal gastritis consistent with Crohn's disease was found in the antrum in 238 (41.5%) patients, including 11 with granulomas. In 56 (9.8%) patients colonization by *H. pylori* was observed. These cases, therefore, remained unclassified with respect to Crohn's disease of the stomach.

Focal gastritis consistent with Crohn's disease was found in the body of the stomach in 113 (37.1%) cases, with granulomas in 6 of these cases. In 48 (11.8%) patients colonization by *H. pylori* was observed, and these also remained unclassified.

In 82 patients gastroscopy was performed at least 1 year before ileocolonoscopy. Focal gastritis consistent

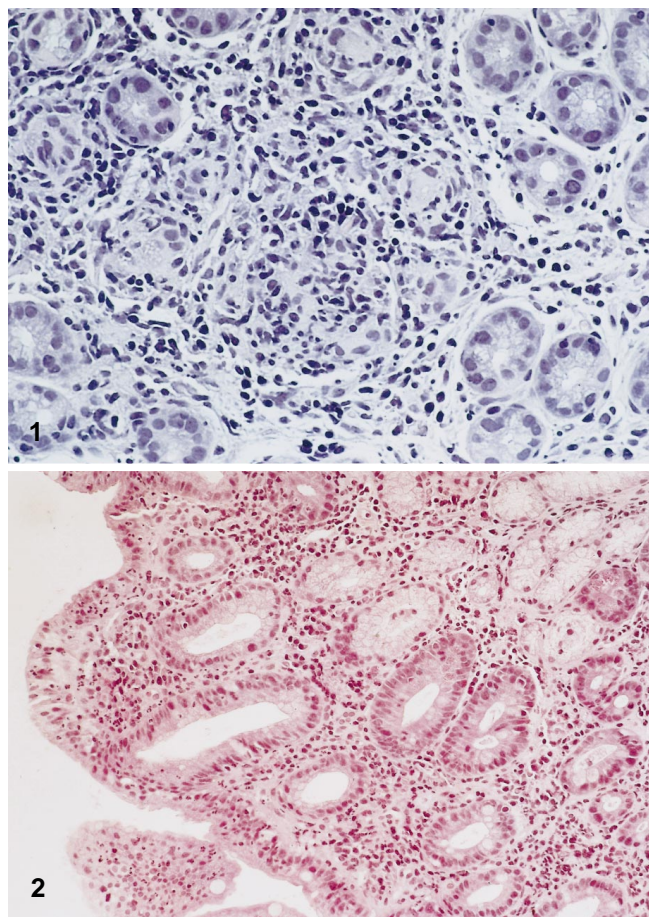


Fig. 1 Focal gastritis typical of Crohn's disease. Note the perifoveolar infiltration and the destruction of the gland in the centre of the lesion. Haematoxylin and eosin, original magnification $\times 300$

Fig. 2 Crohn's disease of the duodenum. Note the flattened villi and the inflammatory infiltrate. Haematoxylin and eosin, original magnification $\times 200$

with Crohn's disease was diagnosed in 32 of these cases (39%), and in 11 of them epithelioid granulomas were found. During follow-up, Crohn's disease of the lower gastrointestinal tract was found in all but 2 cases. Both of these cases were devoid of granulomas in mucosal biopsies of the stomach. The positive predictive value of focal gastritis was 94%.

Further, 50 (61%) cases were free of focal gastritis and were found to have Crohn's disease of the lower gastrointestinal tract at follow-up. The negative predictive value of focal gastritis was 37% in these patients.

Discussion

This study supports the notion that histological lesions diagnostic of Crohn's disease are frequently found in the duodenum, duodenal bulb, antrum and corpus of patients with Crohn's disease. In the duodenum and duodenal

bulb a definitive diagnosis of Crohn's disease was obtained in 12% of our patients. This is in keeping with results obtained by others [14], who reported a 15% incidence of duodenal Crohn's disease. However, our data indicate that Crohn's disease of this part of the small bowel might be even more frequent, and in our material Crohn's disease was suspected in another 15% of the patients. Owing to a lack of more specific histological signs or markers a definitive diagnosis could not be given at the time of examination. The features of gastric Crohn's disease have turned out to be highly specific, and we have shown that focal gastritis suggestive of Crohn's disease is indeed a common feature in patients with Crohn's disease of the small and/or large bowel. Furthermore, we have demonstrated here, for the first time, that the positive predictive value of focal gastritis indicating Crohn's disease is 94%. The negative predictive value, however, is low, as the lesions were only found in less than half of the cases. The percentage of positive cases obtained in this study is comparable to that reported by others, who also found focal gastritis in approximately 50% of their patients [1, 2, 6, 8, 14]. The true incidence of Crohn's disease-associated gastritis, however, is probably higher, as the groups studied also included *H. pylori* positive cases and focal gastritis can only be diagnosed with conviction in *H. pylori* negative patients. Chronic gastritis elicited by *H. pylori*, which is a diffuse type of gastritis, veils the focal gastritis observed in Crohn's disease. An increase in the diagnostic yield can therefore only be obtained after *H. pylori* eradication therapy (M. Stolte, unpublished observation).

Although the positive predictive value of focal gastritis is very high, this type of gastritis is not absolutely specific for Crohn's disease. Especially in cases with a predominance of granulocytes and only a few scattered histiocytes, the gastritis may not be associated with Crohn's disease (unpublished observations), but may be induced by infectious agents other than *H. pylori* or by chemical agents.

In this series 10% of Crohn's disease patients were *H. pylori* positive. A similar figure was given in an earlier report by Halme et al. [6], who found positive *H. pylori* serology in 9.7% of 62 patients analysed. In a study undertaken by El Omar et al. [3] *H. pylori* was found in 22% of patients with inflammatory bowel disease, while *H. pylori* was found in 52% of age- and sex-matched controls. These results suggest that the incidence of *H. pylori* infestation might be lower in patients with inflammatory bowel disease, and long-term treatment with sulphasalazine has been thought to lead to eradication of *H. pylori*. In another series [12], however, the incidence of *H. pylori* was approximately 30%, comparable to that observed in the control group. Although the majority of studies point to a diminished incidence of *H. pylori* infestation in Crohn's disease patients, it is still unclear why or whether this is so.

It is frequently stated that the occurrence of granulomas is the most important histological sign of Crohn's

disease. The low incidence of granulomas reported in this and other studies [6, 14] militates against this opinion. Although granulomas reinforce the diagnosis of Crohn's disease the most important and most frequent histological sign of it is focal inflammation, which mimics the distribution and type of inflammatory lesions present in Crohn's colitis.

In the stomach the focal inflammation is located mainly in the isthmus regions of the foveolae or in the gastric glands. In the duodenum it may be observed in the crypts. According to our present knowledge, an obligatory feature of the focal inflammation is destruction of the glands in the centre of the inflammatory infiltrate, or at least damage to the epithelium, revealed by its cuboidal shape.

A high proportion of Crohn's disease patients have upper gastrointestinal tract involvement, with the most significant lesions found in the antrum, defined by a specific type of gastritis that can easily be identified in routine pathology. We have shown that its positive predictive value is 94%. Our study therefore supports the notion that upper endoscopy with biopsy is a valuable procedure in patients with Crohn's disease, allowing more accurate staging, which may influence therapy. Upper endoscopy with biopsy can also result in the identification of oligosymptomatic patients with the disease when gastric endoscopy is performed as a first diagnostic procedure. Furthermore, it is a useful tool in cases with indeterminate colitis, and may be instrumental in achievement of the correct diagnosis [2, 8].

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