



Gastroenterology in Arab countries

Systematic gastric biopsy in iron deficiency anaemia

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ABSTRACT

Background and study aims: Gastric biopsies are recommended in patients with iron deficiency anaemia to identify atrophic gastritis. However, in practice, only duodenal biopsies are routinely performed. The aim of our study was to determine the value of gastric biopsies in iron deficiency anaemia.

Patients and methods: A prospective study including all patients referred for gastrointestinal endoscopy for iron deficiency anaemia from May 2008 to September 2014 was performed. All patients having endoscopic lesions which may explain occult bleeding were excluded, as well as patients using non-steroidal anti-inflammatory drugs or anticoagulation treatment. Two fundic biopsies, two antral biopsies, and one biopsy from the lesser curve were taken in all patients. Following entities were particularly looked for: chronic gastritis, *Helicobacter pylori* infection, intestinal metaplasia, endocrine hyperplasia and villous atrophy. In cases where intestinal metaplasia was present in the fundus and associated with endocrine hyperplasia and glandular atrophy, immunohistochemical study was performed to confirm autoimmune gastritis.

Results: One hundred seventy-seven patients (mean age 50 years, range: 15–90) were included. Chronic gastritis was found in 149 cases (84%). Infection by *Helicobacter pylori* was found in 107 cases (60%). Fundic intestinal metaplasia was observed in 25 patients (14%) and was associated with *Helicobacter pylori* infection in 52% of cases. Atrophic gastritis was observed in 14 cases (8%) and autoimmune gastritis was confirmed in 5 cases by immunohistochemical study. One patient had on gastric biopsy a carcinoma with signet ring cells.

Conclusion: Intestinal metaplasia was frequently observed and was mostly related to *Helicobacter pylori* infection. These patients require monitoring, especially if they are young because it represents a pre neoplastic condition. However, in our study autoimmune gastritis often described in the literature in case of iron deficiency anaemia was rarely seen raising the question of relative cost-efficiency of fundic biopsies during iron deficiency anaemia.

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Introduction

Current iron deficiency investigation and management guidelines [1] recommend upper endoscopy with systematic gastric biopsies in addition to duodenal biopsies in order to search for *Helicobacter pylori* infection and fundic atrophic gastritis. In Tunisia, gastric biopsies are not systematically performed during upper endoscopy in the work-up of iron deficiency anaemia, and especially if upper endoscopy is normal. Also, the determination of *Helicobacter pylori* status is not systematic if upper endoscopy is

normal. In Habib Thameur's Department, only duodenal biopsies are systematically performed in practice.

The aims of our study were to describe the different histopathologic lesions found in gastric biopsy performed systematically in cases of iron deficiency anaemia, especially atrophic gastritis or auto-immune gastritis and to determine the prevalence of *Helicobacter pylori* infection in these cases.

Patients and methods

Type of study

A prospective study in the Department of Gastroenterology of Habib Thameur hospital in Tunis, Tunisia from May 2008 to September 2014 was conducted.

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Inclusion criteria

All patients referred for gastrointestinal endoscopy for iron deficiency anaemia were included. All patients were informed and provided consent for biopsy taking during endoscopy before procedure. The iron deficiency was confirmed in all patients with a low serum level of iron and a low ferritin level.

Exclusion criteria

All patients with endoscopic lesions that may explain occult bleeding were excluded (patients underwent colonoscopy and gynaecologic examination was done for women), as well as patients treated with non-steroidal anti-inflammatory agents or anticoagulants. Other patients with suspected ileal chronic illness (malabsorption syndrome) were also excluded from the study.

Endoscopic technique

After examination of the oesophageal, fundic, antral and duodenal mucosa, and in addition to the systematically performed duodenal biopsies, both two fundic biopsies, two antral biopsies and one biopsy of the lesser curve of the stomach were performed during upper endoscopy and preserved in 10% formaldehyde solution. Gastric biopsies were performed according to Seattle protocol. A histopathological examination was performed.

Evaluated histological parameters

The specimen were particularly examined for: Chronic gastritis, *Helicobacter pylori* infection, fundic and antral intestinal metaplasia, endocrine hyperplasia and villous atrophy. Gastritis was classified according to the classification of Wyatt and Dixon (Type A: Autoimmune, type B: Due to *Helicobacter pylori* and type C: Due to other causes such as chemical factors) and also to the Sydney system (associating topographic and histologic findings). In cases with intestinal metaplasia in the fundus associated with endocrine hyperplasia and glandular atrophy, immunohistochemical study (anti-intrinsic factor antibodies) was performed to confirm the autoimmune nature of chronic gastritis.

Results

Demographic and biological characteristics of the patients

One hundred seventy-seven patients were included in the study. Mean age was 50 years [range 15–90]. They were 135 women and 42 men (sex ratio = 0.23). An hypochromic microcytic anaemia was detected in all patients with a medium haemoglobin level of 9,2g/dL [range 3,5–11,8], a mean corpuscular volume (MCV) of 73 μ 3 (range 59,9–78,3) and a low haemoglobin amount per red blood cell (HCV) (mean 29,1pg [range 18,2–33,4]). The demographic and laboratory characteristics of the patients are summarized in Table 1.

Table 1
Demographic and laboratory parameters.

Parameter	Mean	Range
Age (years)	50	15–90
Sex	Male/female = 42/135	
Haemoglobin (g/dL)	9,2	3,5–11,8
Mean corpuscular volume (μ 3)	73	59,9–78,3
Haemoglobin amount per red blood cell (pg)	29,1	18,2–33,4

Endoscopic characteristics of patients

Upper endoscopy showed a normal oesophagus in all the patients. Fundic mucosa seemed to be atrophic (Fig. 1) in 14 cases (8%) and was erythematous in 10 cases (6%). In the remaining 153 patients, the fundic mucosa was endoscopically normal. Antral mucosa was erythematous in 27 cases (15%) with a micronodular aspect in 15 cases (8%). An atrophy of duodenal mucosa was detected on upper endoscopy in two cases (1%). In the other cases, duodenal mucosa was normal and no mosaic aspect was found on upper endoscopy. Endoscopic characteristics of our patients are summarized in Table 2.

Histological characteristics of the patients

Chronic gastritis was found in 149 cases (84%). Infection by *Helicobacter pylori* was diagnosed in 107 cases (60%). Fundic intestinal metaplasia was observed in 25 patients (14%) (Fig. 2) and was associated with *Helicobacter pylori* infection in 52%. 44% of patients with fundic intestinal metaplasia were aged less than 50 years. Atrophic gastritis was observed in 14 cases (8%) and autoimmune gastritis was found in 5 cases (2,8%) by the presence of fundic atrophy confirmed by immunohistochemical study. One patient (0,5%) had on gastric biopsy, a signet ring cell carcinoma. Different histological findings are summarized in Fig. 3.

Discussion

In the general population, the prevalence of iron deficiency anaemia can reach up to 8 % in industrialized countries [2,3]. The estimate is from 5 to 30% in pre-menopause women [2]. In post menopause women and men, digestive bleeding is demonstrated in 62–64% of persons presenting with iron deficiency [3]. It is a common cause of referral to gastroenterologists (4–13% of referrals) [4]. Besides coeliac disease which is one of the most frequent causes of iron deficiency anaemia in this context, *Helicobacter pylori* gastritis appears to be the cause of deficiency in certain patients and atrophic gastritis has also been incriminated [5]. Therefore, the guidelines on diagnosis and management of iron deficiency anaemia published in 2011, recommend performing upper and lower GI investigations, which should be considered in all postmenopausal female and all male patients where iron deficiency anaemia has been confirmed unless there is a history of significant overt non-GI blood loss (grade A recommendation) [1].



Fig. 1. Endoscopic aspect of atrophic mucosa of the fundus.

Table 2
Endoscopic findings.

Localisation	Endoscopic findings	n	%
Oesophageal mucosa	Normal	177	100
	Fundic mucosa		
	Atrophic mucosa	14	8
	Erythematous mucosa	10	6
Antral mucosa	Normal	153	86
	Erythematous mucosa	27	15
	Nodular mucosa	15	8
Duodenal mucosa	Normal	130	77
	Atrophic mucosa	2	1
	Normal	175	99

According to these guidelines, all patients should be screened for coeliac disease (grade B recommendation). Also, in patients with recurrent iron deficiency anaemia and normal upper and lower endoscopy results, *Helicobacter pylori* should be investigated and eradicated if present. This suggests that systematic gastric biopsy should be performed (grade C recommendation). In our study, patients had lower endoscopy and gynaecologic examination for

women to exclude colorectal and gynaecologic causes of anaemia. But exploration of the small bowel was not systematically performed. This could represent a limit for our study.

Concerning autoimmune gastritis, it has been identified as a potential cause of iron deficiency anaemia in up to a quarter of cases [6,7] but, although of interest, its diagnosis is currently of little practical value. The concept of gastric atrophy as a cause of iron deficiency anaemia is not new. Achylia gastrica associated with iron deficiency anaemia was described as a clinical entity by Zulficar and achlorhydric gastric atrophy, a synonym for the same entity, has long been recognized as a major cause of iron deficiency anaemia [8–10] but largely forgotten, and completely ignored in subsequent major reports of gastrointestinal causes of iron deficiency anaemia [11,12]. Thus, achlorhydric gastric atrophy was rediscovered by Dickey et al. [13] and information on this condition greatly extended in a series of important studies by Annibale et al [14,15]. Iron absorption is heavily dependent on normal gastric secretion for solubilizing and reducing dietary iron and is impaired by the achlorhydria associated with atrophic gastritis [16]. Age, gender, and severity of disease may be critical in determining whether

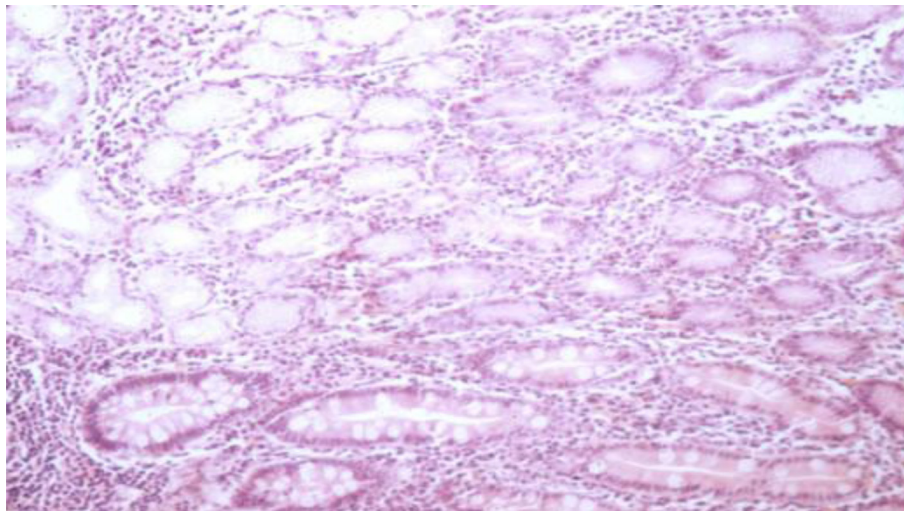


Fig. 2. Histological aspect of intestinal metaplasia of the fundus.

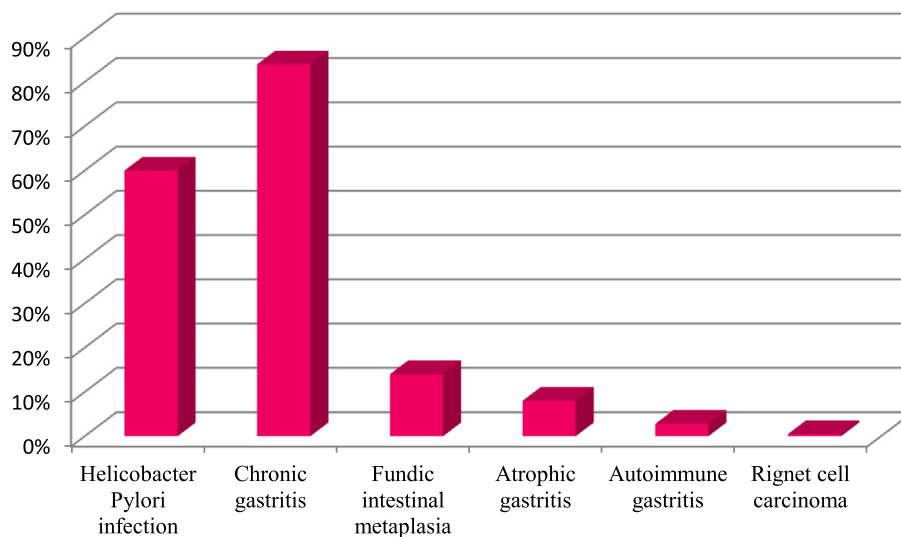


Fig. 3. Histological findings on systematic gastric biopsy.

the clinical presentation is in the form of microcytic iron deficiency anaemia or macrocytic megaloblastic anaemia [17]. In addition, coexistent *Helicobacter pylori* gastritis may be a factor contributing to the development of iron deficiency [18]. It is generally believed that achlorhydric gastric atrophy may precede the clinical onset of pernicious anaemia by many years. Although atrophic gastritis may impair both B12 and iron absorption simultaneously, in young women in whom menstruation represents an added strain on iron requirements, iron deficiency will develop many years before the depletion of B12 stores.

The clinical management of patients with pernicious anaemia includes two different aspects. First, the treatment of cobalamin deficiency and the monitoring of onset of iron deficiency. Second, surveillance to detect early and treat long-term consequences of pernicious anaemia such as gastric cancer and carcinoids [19]. For all these reasons; and even with 1,5% incidence of autoimmune gastritis during our study, systematic gastric biopsies should be performed in iron deficiency anaemia, first to search and eradicate *Helicobacter pylori*, and second, in order to search for autoimmune gastritis. Thus, the best way to evaluate the impact of *Helicobacter pylori* in iron deficiency anaemia would be to eradicate the organism and then to test for serum iron after treatment. In our study, chronic gastritis was found in 101 cases (79%). Infection by *Helicobacter pylori* was diagnosed in 73 cases (52%). Atrophic gastritis was observed in 10 cases (9.1%) and autoimmune gastritis was confirmed in two cases (1,5%) by immunohistochemical study. Our results, confirm those of Kaye and al [7] who evaluated the clinical utility and diagnostic yield of routine gastric biopsies in the investigation of iron deficiency anaemia and who concluded that gastric atrophy was strongly associated with iron deficiency anaemia, and was likely to be causative in some patients and contributory in others. The author recommended performing gastric biopsies, especially from the corpus, which may provide valuable information in the investigation of iron deficiency anaemia. Moreover, in our study, fundic intestinal metaplasia was observed in 15 patients (11.8%) and was associated with *Helicobacter pylori* infection in 60%. An interesting finding is that half of patients with fundic intestinal metaplasia were younger than 50 years and that one patient (0,7%) had on gastric biopsy, a carcinoma with signet ring cells. The percentage of fundic intestinal metaplasia in our work is lower than that reported by Zlatewa et al. who found 48% of metaplasia [20]. The pathogenesis suggested by the authors was that advanced atrophic process was accompanied by increased production of mucous by chief cells and a reduction of the hydrochloric acid-producing parietal cells. With the increase of neutral mucopolysaccharides in the mucous, an increase of acid mucopolysaccharides and the appearance of sulphated complexes follows. As a compensatory and protective reaction of the mucosa metaplasia develops. These results are important as they imply a new surveillance protocol of patients carrying iron deficiency anaemia, especially in patients where intestinal metaplasia is diagnosed, particularly in young patients.

In conclusion, in our study, systematic gastric biopsies in iron deficiency anaemia showed intestinal metaplasia in 11,8% of cases,

which was mostly related to *Helicobacter pylori* infection and which requires monitoring, especially in young patients because it represents a pre neoplastic condition. However, in our study autoimmune gastritis, described in the literature in the case of iron deficiency anaemia was rarely seen (1,5% of cases).

Conflicts of interests

None.

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