Iron deficiency anemia in patients without gastrointestinal symptoms—a prospective study

Eva Niv[a], Avishay Elis[a,d], Rivka Zissin[b,d], Timna Naftali[c], Ben Novis[c,d] and Michael Lishner[a,d]

Niv E, Elis A, Zissin R, Naftali T, Novis B and Lishner M. Iron deficiency anemia in patients without gastrointestinal symptoms—a prospective study. *Family Practice* 2005; **22:** 58–61.

Background and objectives. Chronic gastrointestinal (GI) bleeding is the leading cause of iron deficiency anaemia (IDA) in men older than 50 years and post-menopausal women. There is a scarcity of data regarding IDA patients without GI symptoms or signs. We conducted a prospective study to determine the prevalence and the locations of the GI tract lesions in patients with asymptomatic IDA.

Methods. Forty-eight patients with asymptomatic IDA (25 men older than 50 years and 23 post-menopausal women) underwent colonoscopy, gastroscopy and abdominal computed tomography (CT) with contrast agent.

Results. An anaemia-causing lesion was found in 14 (29%) and 16 (33%) patients in the upper and the lower GI tract, respectively. The prevalence of dual lesions (in both the upper and lower GI tract) was low (6%). In 14 (29%) patients, a malignancy, predominantly right-sided colon carcinoma, was responsible for the IDA. Only one patient had a lesion in the small bowel. In 14 (29%) patients, the work-up was negative.

Conclusion. Our prospective study demonstrates a high rate of malignancy, predominantly right-sided colon carcinoma, in men older than 50 years and post-menopausal women with asymptomatic IDA. This finding obligates a complete and rigorous GI tract examination in this group of patients, especially of the right colon.

Keywords. Asymptomatic, iron deficiency anaemia.

Introduction

Iron deficiency anaemia (IDA) is one of the most common types of anaemia in adults and is a common cause of referral to internal medicine and gastroenterology departments.[1] Chronic gastrointestinal (GI) bleeding is the leading cause of IDA in men above age 50 and post-menopausal women.[1–3] In patients with site-specific symptoms, the sequence of diagnostic testing is guided by the symptoms.[4,5] However, the approach to patients with IDA without GI symptoms is controversial due to a lack of data regarding the types and the locations of the lesions. Both American and European guidelines for the evaluation of asymptomatic IDA recommend performing colonoscopy and/or oesophagogastroduodenoscopy (EGD) in an arbitrary order.[4,5]

Previous studies included heterogenous study groups, such as patients with and without GI symptoms, various ages, pre- and post-menopausal women and iron deficiency with or without anaemia.[6–17] There are only a few studies that specifically evaluated asymptomatic IDA,[18,19] but none of them addressed asymptomatic IDA in men older than 50 years or post-menopausal women. However, the aetiology and frequency of the GI tract lesions in this subset of patients may differ from those of other groups. Therefore, we designed a prospective study to determine the prevalence and location of GI tract lesions in men older than 50 years and post-menopausal women with asymptomatic IDA.

Methods

The study was conducted prospectively from August 1999 to August 2001 at Meir Hospital, Israel. Men >50 years old and post-menopausal women with

asymptomatic IDA, who were hospitalized at the Department of Medicine or evaluated at the Gastroenterology Department, were screened for enrolment into the study. The hospitalized patients were admitted due to either anaemia or other causes, and IDA was found during the evaluation. The patients in the Gastroenterology Department were referred by their primary care physicians for the evaluation of IDA.

IDA was defined as a haemoglobin level ≤12 g/dl in men or ≤11 g/dl in women with a serum iron level <50 μg/dl, accompanied by a serum ferritin level <30 ng/dl or a serum transferrin level >360 mg/dl. A detailed history was obtained by interview, focusing on GI symptoms, medications and chronic diseases. A complete physical examination was performed. Only asymptomatic post-menopausal women and men >50 years old were considered as possible candidates for the study.

Exclusion criteria included (i) site-specific symptoms such as dyspepsia, diarrhoea, abdominal pain or constipation; (ii) site-specific signs on physical examination; (iii) active GI bleeding; (iv) extraintestinal bleeding, such as vaginal or urinary tract bleeding; (v) known active or chronic GI diseases; (vi) previous gastrectomy or any bowel resection; (vii) inadequate diet; (viii) warfarin treatment; (ix) mental or psychiatric disorder; or (x) contraindications to GI tract endoscopy or computed tomography (CT) scan. The use of aspirin or non-steroidal anti-inflammatory drugs (NSAIDs) and general symptoms of anaemia were not considered as exclusion criteria. The finding of occult blood in stool was not considered as either an inclusion or an exclusion criterion.

All patients underwent colonoscopy and EGD. As an additional test, abdominal CT scan with contrast agent was performed. The sequence of these tests was arbitrary, but they were performed within a short period of time, usually 2 weeks.

Endoscopies were performed using standard video endoscopes (Pentax, model EG 2940, EC 3840L, Japan). Duodenal biopsies were taken during EGD, while gastric biopsies were also performed when gastritis was suspected. In all colonoscopies, the caecum was intubated.

CT scans were obtained on an Elscint 2400 Elite (non-helical scanner) or a Picker MX Twin-flash (hellical scanner) with 8.8–10 mm collimindion and pubis and a 0.8–1 cm interval from the diaphragm to the symphysis.

The following abnormalities of the GI tract were considered as potential causes of IDA: erosive oesophagitis, hiatal hernia with erosions, erosive gastritis, atrophic gastritis, gastric and duodenal ulcers, gastric tumours, erosive duodenitis, coeliac disease and other malabsorptive diseases, small intestinal tumours, inflammatory bowel diseases, colorectal tumours, angiodysplasia and colonic polyps >1 cm.

All patients provided an informed consent. The study protocol was approved by Helsinki human rights committee of Meir Hospital.

Analysis of the diagnostic yield of invasive and non-invasive tests in this cohort of patients has been published in the *American Journal of Medicine*.

Statistical analysis
Differences in the prevalence of upper GI findings among users and non-users of aspirin or NSAIDs, as well as differences in haemoglobin levels, gender and age of patient with and without malignancy were assessed by the chi square test for categorical variables and the Student's t-test for continuous ones.

Results

Forty-eight patients, 25 men older than 50 years and 23 post-menopausal women, met the predefined inclusion criteria of asymptomatic IDA and were enrolled in the study. None of the patients who met the inclusion criteria refused to participate. The demographic parameters of the patients and the parameters of IDA are provided in Table 1. Fourteen patients used aspirin (100 or 325 mg) and only one took a non-selective NSAID. No complications of EGD, colonoscopy or abdominal CT scan were recorded.

Table 2 provides the causes of IDA. Altogether, endoscopies and abdominal CT detected the cause of IDA in 34 patients (71%). Fourteen (29%) patients had a lesion which explained their anaemia in the upper GI tract alone, 16 (33%) in the lower GI tract alone, three (6%) had lesions in both upper and lower GI tract

TABLE 1 *Demographic characteristics and laboratory data of the patients with asymptomatic IDA*

Total number	48
Male/female	25/23
Median age (years)	75
Smokers	12
Aspirin users	14
Non-selective NSAID users	1
Alcohol abusers	1
Haemoglobin (g/dl)	
Median	9
Range	5–11.8
Iron (μg/dl)	
Median	17
Range	7–41
Transferrin (mg/dl)	
Median	410
Range	360–437
Ferritin (ng/dl)	
Median	13
Range	5–22

TABLE 2   *The aetiological causes of IDA in the study group*

Endoscopic studies	
Upper GI tract	
Oesophagitis	2
Diaphragmatic hernia + erosions	2
Erosive gastritis	2
Atrophic gastritis	7
Erosive duodenitis	1
Duodenal ulcer	1
Carcinoma of stomach	2
Lower GI tract	
Colonic polyps	5
Angiodysplasia	3
Colon carcinoma	10
Additional studies (CT scan)	
Small intestine tumor	1
Colon carcinoma[a]	1

[a] This was missed by the first colonoscopy and was confirmed by second one.

and one patient had a lesion in the small intestine. In 14 (29%) patients, the work-up was negative. In 14 (29%) patients, a malignancy was responsible for the IDA. Eleven patients had adenocarcinoma of the colon (in 10 cases it was located in the caecum and the ascending colon and in one case in the sigma). Two patients had adenocarcinoma of the stomach and one had a malignant tumour of the small intestine. Five colonic polyps, removed during colonoscopy, were tubular and tubulo-villous adenomas low-grade dysplasia.

Three patients (6%) had lesions in both the upper and lower GI tract. One patient had an active duodenal ulcer and adenocarcinoma of the colon, a second patient had atrophic gastritis and a tubular colonic polyp >1 cm, and the third had gastric adenocarcinoma and a tubulo-villous colonic polyp >1 cm.

The prevalence of upper GI tract findings was similar among the 15 patients who used aspirin or NSAIDs and the non-users ($P = 0.09$). The only patient with active peptic ulcer did not receive aspirin or an NSAID.

The mean haemoglobin level in patients with malignancies was not significantly different from that in those who did not (8.76 versus 8.62 g/dl, $P = 0.774$). There was no significant diference in the age of patients having malignant tumours and those with non-malignant causes of IDA (71 ± 8 versus 76 ± 8 years, $P = 0.05$). Although 10 of 14 patients with malignancy were males as compared with 15 of the 34 patients in the non-malignancy group, this difference was not statistically significant ($P = 0.085$).

Discussion

In this prospective study, we found a high rate of malignancy, predominantly right-sided colon carcinoma,

among men older than 50 years and post-menopausal women with asymptomatic IDA (29% of the patients). A similar rate of upper and lower GI tract lesions alone (29 and 33%, respectively) and a relatively low rate of dual lesions (6%) were demonstrated. Only one patient had a lesion in the small bowel. In almost one-third of the patients, the work-up was negative.

Although IDA is a very common clinical problem, most reported studies comprised a surprisingly small and heterogenous cohorts of patients with variable demographic and anaemia parameters.[6–17] In general, in 7.7–47% of patients in these studies, the cause of IDA remained unidentified. About 25–46% of patients had an anemia-causing lesion in the upper GI tract alone, 17–27% in the lower GI tract only, 1–29% in both the upper and lower GI tract and 0–6% in the small bowel. The malignancy rate ranged from 7 to 51%. This high variability is explained by the heterogeneous population of patients in these studies. In contrast, we focused on a homogenous group of men older than 50 years old and post-menopausal women with asymptomatic IDA in whom extraintestinal blood loss was carefully ruled out.

Wilcox *et al*.[18] and Annibale *et al*.[19] published the only studies regarding asymptomatic iron deficiency. Wilcox *et al*. included patients with IDA, as well as iron deficiency without anaemia. They identified a potential cause of iron deficiency in 44% of patients (21% colonic carcinoma, 17% vascular ectasia, 2% gastric carcinoma, 2% colonic ulcers and 2% colonic polyps).[18]

Annibale *et al*. included only patients with IDA, but the age range of their patients was very wide (18–80 years), including pre-menopausal women. They identified an anaemia-causing lesion in 85% of patients, mostly in the upper GI tract, and 8% had findings in both the upper and lower GI tract. Seventeen percent had a malignancy (14% colon and 3% gastric cancer). The higher rate of upper GI tract lesions and lower rate of malignancy, as well as the finding of coeliac disease in four patients and Crohn's disease in one patient can be explained by their younger cohort.[19]

In almost one-third of the patients in our study group, the work-up was negative. This rate of negative work-up is similar to previous studies, which did not use a capsule video endoscopy of the small bowel.[6–19] The future use of this technique will probably decrease the unexplained cases of IDA.

We found no correlation between the haemoglobin levels in patients with and without malignancy. It is commonly accepted that the haemoglobin and ferritin levels reflect the duration and the severity of occult GI bleeding rather than the presence of specific pathology.

The main limitation of our study is the relatively small number of patients studied. Another limitation is that we did not include video capsule or virtual colonoscopy studies in patients with negative work-up. However, the study was a prospective study with carefully designed

inclusion criteria. Thus it provide valuable information regarding a very homogenous cohort of patients.

In conclusion, a relatively high rate of malignancies as a cause of asymptomatic IDA obligates a complete and rigorous GI tract examination in men older than 50 years and post-menopausal women. An almost equal prevalence of anaemia-causing lesions in the upper and lower GI tract demonstrates that both parts of the GI tract are equally suspicious. Considering the fact that most tumours in this age group are found in the right colon, colonoscopy should probably be the first diagnostic procedure. Small bowel investigation should be considered in the case of refractory IDA and otherwise negative work-up.

Declaration

References

[1] Looker AC, Dallman PR, Carroll MD *et al*. Prevalence of iron deficiency anemia in the United States. *J Am Med Assoc* 1997; **277:** 973–976.

[2] Andrews NC. Disorders of iron metabolism. *N Engl J Med* 1999; **341:** 1986–1995.

[3] Rockey DC. Occult gastrointestinal bleeding. *N Engl J Med* 1999; **341:** 38–46.

[4] Goddard AF, McIntyre AS, Scott BB. Guidelines for the management of iron deficiency anaemia. *Gut* 2000; **46 (Suppl IV):** iv1–iv5.

[5] AGA technical review on the evaluation and management of occult and obscure gastrointestinal bleeding. *Gastroenterology* 2000; **118:** 201–221.

[6] Reyes LA, Gomez CF, Galvez CC, Mino FG. Iron-deficiency anemia due to chronic gastrointestinal bleeding. *Rev Esp Enferm Dig* 1999; **91:** 345–358.

[7] Kepczyk T, Kadakia SC. Prospective evaluation of gastrointestinal tract in patients with iron-deficiency anemia. *Dig Dis Sci* 1995; **40:** 1283–1289.

[8] Lindsay JO, Robinson SD, Jackson JE, Walter JR. The investigation of iron deficiency anemia—a hospital based audit. *Hepatogastoenterology* 1999; **46:** 2887–2890.

[9] Zuckerman G., Benitez J. A prospective study of bidirectional endoscopy (colonoscopy and upper endoscopy) in the evaluation of patients with occult gastrointestinal bleeding. *Am J Gastroenterol* 1992; **87:** 62–66.

[10] Gordon SR, Smith RE, Power GC. The role of endoscopy in the evaluation of iron deficiency anemia in patients over the age of 50. *Am J Gastroenterol* 1994; **89:** 1963–1967.

[11] Hardwick RH, Amstrong CP. Synchronous upper and lower gastrointestinal endoscopy is an effective method of investigating iron-deficiency anemia. *Br J Surg* 1997; **84:** 1725–1728.

[12] Bampton PA, Holloway RH. A prospective study of the gastroenterological causes of iron deficiency anemia in a general hospital. *Aust NZ J Med* 1996; **26:** 793–799.

[13] Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med* 1993; **329:** 1691–1695.

[14] Willoughby JM, Laitner SM. Audit of the investigation of iron deficiency anaemia in a district general hospital, with simple guidelines for future practice. *Postgrad Med J* 2000; **76:** 218–222.

[15] Moses PL. Smith RE. Endoscopic evaluation of iron deficiency anemia. A quide to diagnostic strategy in older patients. *Postgrad Med* 1995; **98:** 213–216.

[16] McIntyre AS, Long RG. Prospective survey of investigation in outpatients referred with iron deficiency anemia. *Gut* 1993; **34:** 1102–1107.

[17] Rockey DC, Koch J, Cello JP *et al*. Relative frequency of upper gastrointestinal and colonic lesions in patients with positive fecal occult-blood test. *N Engl J Med* 1998; **339:** 153–159.

[18] Wilcox CM, Alexander LN, Clark WS. Prospective evaluation of the gastrointestinal tract in patients with iron deficiency and no systemic or gastrointestinal symptoms or signs. *Am J Med* 1997; **103:** 405–409.

[19] Niv E, Elis A, Zissin R et al. Abdominal computed tomography in the evaluation of patients with asymptomatic iron deficiency anemia: a prospective study. *Am J Med* 2004; **117:** 193–195.