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Endoscopic evaluation of gastrointestinal tract lesions in patients with iron-deficiency anemia

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Abstract

AIM: To prospectively evaluate the relation of gastrointestinal lesions and iron-deficiency anemia (IDA) caused by gastrointestinal tract bleeding.

METHODS: Sixty-one patients with IDA caused by gastrointestinal tract bleeding were included in our study. Lesions were detected by esophagogastroduodenoscopy (EGD) and/or colonoscopy. Histories of upper gastrointestinal tract symptoms, including pyrosis, dysphagia, upper abdominal pain, dyspepsia, nausea and vomiting, and lower gastrointestinal tract symptoms such as changes in bowel habits, constipation, diarrhea and lower abdominal pain, were obtained from each patient. History of NSAID drugs intake was also obtained. Each patient underwent complete physical examination and fecal occult blood test (FOBT) of three spontaneously passed stools or of stool samples obtained by digital rectal examination. All the patients completed testing for complete blood count, total iron-binding capacity, and serum ferritin level. Some patients underwent bone marrow aspiration to examine the iron stores.

RESULTS: The 61 patients included 35 men and 26 women, with mean age of 53.6 years (range of 18-67 years). The mean hemoglobin level was 82-19 g/L and the mean ferritin level was 8.9 ± 4.8 μmol/L. In the 10 patients diagnosed with concomitant inflammatory conditions, the ferritin levels were lower, ranging between 1.8 μmol/L and 4.2 μmol/L, and the patients showed an elevated white blood cell count. The mean transferritin saturation was 6.8% ± 4.2%. Bone marrow aspiration was performed on 5 patients to confirm IDA. The upper endoscopic findings of 43 patients with IDA included gastric erosions (n = 10), esophagitis (n = 8), gastric cancer (n = 6), gastric ulcer (n = 8), duodenal ulcer (n = 9), gastric polyps (n = 1) and esophageal cancer (n = 1). Colonoscopic findings of 18 patients with IDA included colon cancer (n = 2), colon polyp (n = 6), ulcerative colitis (n = 9), and Crohn's colitis (n = 1). Five of the total 61 (8.2%) patients had lesions in both the upper and lower gastrointestinal tract that met our criteria for potentially causing IDA.

CONCLUSION: Combined application of EGD and colonoscopy is able to identify potential bleeding sources in most patients with IDA.

Key words: Anemia, iron-deficiency; Gastrointestinal hemorrhage; Endoscopy

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INTRODUCTION

Iron-deficiency anemia (IDA) caused by gastrointestinal tract bleeding very commonly occurs in 3.5%-5.3% of adult men and postmenopausal women[1], and in 7% of hospitalized geriatric in-patients[2]. Among patients over 65 years old with anemia, 36%-70% have IDA[3]. Gastrointestinal tract pathology has proven that IDA patients account for 27%-95%[1,4]. Studies that have overestimated the prevalence of gastrointestinal tract pathologies causing IDA have reported lesions such as esophageal varices, prior gastric surgery, and the use of nonsteroidal anti-inflammatory drugs (NSAIDs) without documented gastropathy, all of which cannot actually cause IDA[1,4-6]. In contrast, other studies may have underestimated the prevalence according to use of findings from primarily radiologic evaluation or incomplete upper and lower gastrointestinal tract examinations[1,4]. Furthermore, still other studies have evaluated patients with positive fecal occult blood test (FOBT) with or without IDA[2] or have primarily evaluated the upper gastrointestinal tract lesions in 21%-59% of patients with all types of anemia including IDA, reporting incidence of upper gastrointestinal tract lesions in 21%-59% of the patients[2,7-9]. In a recent prospective study by Rockey and Cello[6], all 100 patients with IDA showed negative endoscopic results; however, since the authors did not obtain small bowel biopsies they were unable to exclude celiac disease.

Therefore, the aim of our study was to prospectively evaluate the gastrointestinal tract pathology in patients with IDA using

Table 1 Upper GI endoscopic findings of 43 patients with iron-deficiency anemia

Lesion	Patients, *n*
Gastric erosions	10
Esophagitis	8
Gastric cancer	6
Gastric ulcer	8
Duodenal ulcer	9
Gastric polyps	1
Esophageal cancer	1
Total lesions	43

Table 2 Colonoscopic findings of 18 patients with iron-deficiency anemia

Lesion	Patients, *n*
Colon cancer	2
Colon polyp	6
Ulcerative colitis	9
Crohn's colitis	1
Total lesions	18

Table 3 Findings of 5 patients with both upper and lower gastrointestinal tract lesions and iron-deficiency anemia

Patient	Upper gastrointestinal tract lesion	Lower gastrointestinal tract lesion
1	Esophagitis	Ulcerative colitis
2	Esophagitis	Cancer
3	Duodenal ulcer	Colon polyp
4	Duodenal ulcer	Cancer
5	Gastric cancer	Colon polyp

a combination of esophagogastroduodenoscopy (EGD) and colonoscopy.

MATERIALS AND METHODS

All of the patients included in this study had a history of upper gastrointestinal tract symptoms, including pyrosis, dysphagia, upper abdominal pain, dyspepsia, nausea and vomiting, and/or lower gastrointestinal tract symptoms such as changes in bowel habits, constipation, diarrhea, and lower abdominal pain. History taking included use of NSAIDs. Each study participant underwent complete physical examination and FOBT of three spontaneously passed stools or of a stool sample obtained by digital rectal examination. All the patients underwent testing to determine complete blood cell counts, total iron-binding capacity, and serum ferritin level. Some patients underwent bone marrow aspiration to examine iron stores.

Anemia was defined as hemoglobin (Hb) levels of < 120 g/L in men and < 110 g/L in women, according to the World Health Organization criteria combined with the general conditions (affecting anemia) particular to populations of the Lanzhou city region. Specifically, IDA was diagnosed according to absence of detectable (stainable) iron in the bone marrow aspirates or a combination of concentration of serum ferritin at < 13 μmol/L (below the normal range of 13-31 μmol/L), of serum iron at < 45 μmol/L (below the normal range of 45-73 μmol/L) and of transferritin saturation at < 20% (below the normal range of 20%-55%). Ferritin is an accepted marker of iron stores, with levels of 1.8-3.6 μmol/L indicating iron deficiency[3,7]. Patients with IDA and inflammatory conditions present with serum ferritin levels elevated to 8.7-10.4 μmol/L[7]. Therefore, in this study, in patients with inflammatory conditions, serum ferritin < 8.7 μmol/L in association with red blood cell mean corpuscular volume of < 80% and transferritin saturation of < 10% was considered diagnostic of IDA.

Patients were excluded from our study based upon the following: previous evaluation for IDA; women with symptoms of premenopause; current diagnosis of gastrointestinal cancer, hemoglobinopathy or renal failure; recent experience of surgery, trauma or acute gastrointestinal bleeding; any previous gastric surgery. For this study, the following lesions were considered as potential causes of IDA: EGA-detected lesions of esophagitis with multiple linear erosions and/or ulcers in the distal 2 cm or more of the esophagus with or without active bleeding, gastritic erosions defined as breaks in mucosa covered with thick exudates of 2 mm and 5 mm, gastric ulcer or duodenal ulcer > 10 mm, esophageal cancer, gastric cancer, polyps > 1 cm; colonoscopy-detected lesions of colorectal cancer, polyps > 1 cm, bleeding hemorrhoids defined by 15-30 mL of blood loss for an average of three times a week for over 6 mo.

From 1991 to 1994, 61 of a total of 73 patients with IDA who underwent EGD and/or colonoscopy met the above-mentioned criteria for study inclusion. The IDA treatment administered (endoscopy-based) was safe and effective for most of these patients. The treating hospital was dependent on EGD or colonoscopy for management of IDA patients for the study years based upon the demonstrated safety and cost benefits.

RESULTS

A total of 73 patients showed gastrointestinal tract lesions under endoscopy during our study period. Sixty-one (83.6%) of those 73 patients showed lesions endoscopically that were considered responsible for their IDA according to our criteria described above. However, 12 (16.4%) of the total 73 patients showed endoscopic lesions that did not meet our criteria, resulting in those lesions not being considered as causative of the patient's IDA. All the 61 patients (35 men and 26 women) with gastrointestinal tract bleeding associated with IDA were included in the study. The mean age was 53.6 years, with a range encompassed by 18.67 years. The mean Hb was 82 ± 19 g/L ($\bar{x}$ ± s). The mean ferritin was 8.9 ± 4.8 μmol/L. In the 10 patients who presented with inflammatory conditions, the ferritin was lower, ranging from 1.8-4.2 μmol/L, and they showed increased white blood cell count and decreased mean corpuscular volume. The mean transferritin saturation was 6.8% ± 4.2%. Bone marrow aspiration was performed to confirm IDA in 5 patients.

EGD showed potentially bleeding lesions in 43 of the total 61 (70.5%) study participants (Table 1). Gastric erosions were the most common lesions found in the upper gastrointestinal tract, accounting for 10 of 43 (23.5%) of the detected lesions, followed by erosive and/or peptic ulcers, which were found in 17 of the 43 (39.5%) lesions. Only one patient with Crohn's disease showed signs of terminal ileal Crohn's disease by colonoscopy.

Colonoscopy showed potentially bleeding lesions in 18 of the 61 (29.5%) study participants (Table 2). Ulcerative colitis was the most common lesion. The location of cancers was rectum for 2 patients (both, Duke's stage B1). Three patients with internal hemorrhoids were bleeding more than 60 mL of blood over three times a week for more than 6 mo. Five (8.2%) of the total 61 patients had lesions in both upper and lower gastrointestinal tracts that met our criteria for potentially causing IDA. In these patients, either the upper or the lower gastrointestinal tract lesions, or both, were considered as having the ability to lead to IDA-causative bleeding. The endoscopic findings of these patients are summarized in Table 3.

Symptomology among the 61 study participants included upper gastrointestinal tract symptoms (n = 30), lower gastrointestinal tract symptoms (n = 14), and combined upper and lower symptoms (n = 5). All of the patients with upper and/or lower gastrointestinal tract symptoms showed upper and/or lower gastrointestinal tract lesions upon examination, but only 27 (44.3%) had positive results on FOBT [the res, 34 (55.7%), had negative results on FOBT]. There was no significant difference between the FOBT-positive group of patients and the FOBT-negative group of patients in regard to the location of the detected IDA-causative lesions (P > 0.05). The sensitivity and specificity of FOBT for detecting a, IDA-causative lesion was 49.8% and 61.2% respectively, and the positive predictive value was 75.2%. The sensitivity, specificity and positive predictive value of FOBT for detecting colorectal neoplasms (polyps as well as cancers) were 61.6%, 61.6% and 56.6% respectively. FOBT gave positive results for 6 of the 9 patients with gastrointestinal tract cancers. FOBT gave positive results for 4 patients with colon cancer, but negative results for 3 patients with gastric cancer.

Fourteen (22.9%) patients took NSAIDs on a regular basis, and

13 patients had upper or lower gastrointestinal tract lesions that were potentially caused by the NSAID use and included esophagitis, gastric erosions, gastric ulcer, duodenal ulcer, and colon lesions. Forty-seven (77%) patients were not taking NSAIDs and had lesions associated with IDA. Forty-six patients participated in follow-up study (15 patients did not participate in follow-up), and IDA was cured in 29 of the 46 followed-up patients.

DISCUSSION

IDA is believed to result from chronic gastrointestinal tract blood loss. The reported prevalence of gastrointestinal tract lesions in patients with IDA has varied significantly from study to study. This general discrepancy may be due to incomplete evaluation of both upper and lower gastrointestinal tracts, the retrospective nature of the studies, inclusion of radiologic evaluation instead of endoscopic evaluation, a heterogenous patient population and their distinctive (but un-analyzed) characteristics, and/or lack of precise definition of the IDA-causative lesions[4,9]. In this study, we included lesions that have been well-described in the literature as resulting in chronic or intermittent blood loss that is causative of IDA[6]. We included mucosal lesions that lead to bleeding, such as esophagitis, gastritis, gastric erosions, and gastric and duodenal ulcers[6]; the latter were the most common IDA-causing lesions detected in our patients by both EGD and colonoscopy, similar to the findings by Rockey and Collo[6]. IDA, however, may be the initial presentation of gastrointestinal tract cancer[10]. In our study, diagnosis of cancer (by the gastrointestinal endoscopic evaluations) was made in 8 of the patients, representing a percentage (13.1%) of the study population that is similar to that reported previously (6%-28%)[1]. In particular, Rockey and Cello[6] reported finding 12 cancers in a prospective evaluation of 100 patients with IDA.

Zoli *et al*[11] investigated whether serum transferrin receptors (sTfRs) were affected by rheumatoid arthritis (RA), in order to verify a possible relationship with the degree of anemia and with the severity of the inflammatory disease. The authors reported that, in patients with RA, sTfR levels were significantly higher than those in the normal control group but lower than those in iron-deficient anemic patients, and that this feature correlated positively with erythrocyte sedimentation rate and IL-1beta and negatively with Hb. Further analysis was conducted with anemic patients with RA divided into two groups, with group A (56%) having a possible iron deficiency (total serum iron < 2.7 and ferritin < 8.7 μmol/L) and group B having no observable iron deficiency (total serum iron > 16 and ferritin > 8.7 μmol/L). No significant difference in sTfR was observed between the two groups. Thus, sTfR was elevated and related to the degree of anemia and to the inflammatory process in RA. The authors concluded that reduced sTfR levels in patients with RA, as compared with patients with iron-deficiency anemia, may indicate a reduced erythropoietic activity in RA. Indeed, it has been reported that the bioavailability of iron from a habitually consumed diet can affect this process; specifically, a study compared the diets of pre-adolescent children of low socio-economic status with supplementation of an additional 8 g of protein supplied by 34 g of legumes (Green gram and Moth bean ratio of 1:1) and of anemic rats with supplementation of 195 mL of buffalo's milk. In the latter, the bioavailability of iron for hemoglobin regeneration relative to $FeSO_4$ was 69.5%, as compared with 47.5% in the former; the legume supplementation showed no improvements for the pre-adolescent children of low socio-economic status[12].

Anemia is usually difficult to correct in kidney transplant recipients, likely because of an iron deficient or inadequate erythropoietin (Epo) production status post-transplantation. Moore *et al*[13] evaluated the effects of iron (Fe) availability on correction of anemia in renal transplant recipients and sought to characterize patterns of early Epo production by transplanted kidneys as related to peri-transplant factors. In a prospective randomized trial, 51 consecutive renal transplant patients were followed-up for 6 mo. Epo was measured on days 0, 3, 14, 48 and 168 post-transplantation. Fe status was monitored on days 14, 48 and 168. Patients were randomized on day 14 based on Fe status. Iron-deficient (FeD) patients (n = 24) were randomized to receive daily Fe supplementation (FeDs; n = 12) or no supplementation (FeDns; n = 12). Those with normal Fe status (FeN; n = 27) were followed as controls. No differences were found between groups on day 0 for hematocrit, creatine, Epo, age, dialysis history, or type of donor. On day 3, the creatine and hematocrit levels were similar among the groups, while only Epo was significantly higher in the FeD group (*vs* FeN, $P < 0.004$); this higher level persisted to the end of the study. Although the hematocrit improved in each patient over the study period, most of the FeDs and FeN group members were anemic and Fe deficient at the end of 6 mo; all FEDs patients, however, had corrected their anemia ($P < 0.009$) and Fe status by study end. Four FeDs patients developed polycythemia. Epo production correlated inversely to cold ischemia time in cadaver renal allografts ($P < 0.008$). One-hundred-and-fourteen female pediatric patients (aged 11-14 years) from Wembley, Middlesex, were assessed for Fe status (*via* Hb), packed cell volume, mean corpuscular Hb concentration, height, weight, eating habits and ethnic origin, and undertook a step test to assess physical performance. Twenty-percent of the total of girls had Hb < 120 g/L, ranging from 11% in girls of white ethnicity to 22%-25% in girls of Asian origin. Prevalence of low Hb was 20% in vegetarians, being higher in white vegetarians compared with non-vegetarians (23% *vs* 4%) but lower in Indian vegetarians compared with non-vegetarians (17% *vs* 32%). Low Hb was present in 25% of girls who had tried to lose weight in previous years, and was more common in girls from manual laborer social class status than non-manual laborer status (24% *vs* 10%). At the start of the step test, 23 girls with low Hb had heart rates similar to those with normal Hb, but heart rates in the low Hb group were significantly elevated immediately after the step test, and the rate was still significantly elevated 1 min later. The results from the present study agree with the findings of this previous study in girls of white ethnicity, and suggest that physical performance may be compromised at mild levels of anemia[14].

Gastrointestinal bleeding is believed to cause IDA. Kepezyk *et al*[5] reported on 70 patients with IDA that underwent EGD and colonoscopy; patients with unremarkable findings by these two methods then underwent small bowel biopsy by EGD to determine the presence of celiac disease. Enteroclysis was performed if this further evaluation was negative. Endoscopic results showed that at least one lesion potentially accounted for the IDA in 50 (71%) of the patients. Colonoscopic results showed that 21 (30%) of the patients had 22 lesions (including 4 cases of colon cancer, 7 of adenoma > 1 cm, 6 of vascular malformation, 4 of severely bleeding hemorrhoids, and 1 of ileal Crohn's disease). At EGD, 39 (56%) of the patients were found to have 43 lesions, including 11 of gastric erosion, 10 of esophagitis, 4 of vascular malformation, 4 of celiac disease, 3 of gastric cancer, 3 of gastric ulcer, 3 of duodenal ulcer, 2 of gastric polyp > 1 cm, 1 of duodenal lymphoma, 1 of esophageal cancer, and 1 of duodenal Crohn's disease. Twelve (17%) of the patients had both upper and lower gastrointestinal tract lesions. Twenty-four (75%) of the 32 patients with positive FOBT results had potentially bleeding lesions, as compared with 24 (63%) of the 38 patients with negative FOBT results ($P > 0.05$). Six of the 9 patients with malignancy had positive FOBT. Twenty patients with normal endoscopic findings and who underwent small bowel biopsy had normal enteroclysis results. It is thus concluded that the combination of colonoscopy and EGD identifies potential bleeding sources in most patients with IDA. In the absence of a potentially bleeding lesion, small bowel biopsy during EDG is essential to diagnose celiac disease.

Aspirin or NSAIDs can cause esophagogastroduodenopathy, which itself has been associated with an increased frequency of IDA. However, our study shows that the prevalence of endoscopic findings causing IDA is not similar among patients who have taken NSAIDs and those who have not (22.9% *vs* 77.1%). In contrast, Rockey and Cello[6] found no correlation between the use of NSAIDs and lesions in the upper gastrointestinal tract. In our study, some of the patients with NSAIDs-related upper gastrointestinal tract lesions also had colonic lesions that were determined to be the actual IDA-causing lesions. These findings indicate that evaluation of IDA patients taking NSAIDs should not be limited to the upper gastrointestinal tract only. It is possible that many patients who

have ingested NSAIDs may not voluntarily supply the information concerning their history of taking NSAIDs. This possibility was clearly shown to be true in a recent study by Lanas *et al*[15], wherein the objective evidence of platelet cyclooxygenase inhibition revealed a large number of patients with acute upper and lower gastrointestinal bleeding who failed to report use of aspirin or NSAIDs. It is also possible that in some of the patients, the NSAID-unrelated lesions in elderly patients, either in the upper gastrointestinal tract or the lower gastrointestinal tract, may bleed acutely or chronically due to antiplatelet aggregation properties of the NSAIDs or aspirin[5,16]. Finally, some patients with IDA may have small bowel lesions induced by NSAIDs that may lead to bleeding chronically.

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