Lesson of the Week

Gastrointestinal investigation of iron deficiency anaemia

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The most common cause of microcytic, hypochromic anaemia in Western society is iron deficiency.¹ In men and postmenopausal women iron deficiency usually results from chronic blood loss.^{2,4} Ulcerative oesophageal, gastric, or duodenal lesions are commonly detected endoscopically in patients with iron deficiency anaemia, who are often taking non-steroidal anti-inflammatory drugs.^{3,4} Although patients with right sided colonic cancer may present with iron deficiency anaemia, it is not known how commonly such lesions or other colonic diseases coexist in anaemic patients with a benign upper gastrointestinal lesion. Consequently there are no firm guidelines on whether colonic assessment is warranted in these patients. Our aims, therefore, were to determine whether patients with iron deficiency anaemia and benign upper gastrointestinal lesions on endoscopy require colonic assessment; whether the absence of specific colonic symptoms in these patients obviates the need for colonic investigation; and to what extent upper and lower gastrointestinal symptoms can predict the presence of upper and lower gastrointestinal lesions in patients with iron deficiency anaemia.

Patients and methods

The haematological results of all inpatients at this hospital for the 17 months from May 1983 to October 1984 were prospectively screened. Those with a haemoglobin concentration less than 110 g/l and a mean corpuscular volume less than 80 fl were selected for assessment.

Patients were excluded from the study if general debility precluded any investigation or if they were 85 years or older; had confirmed malignancy at the time of admission; had a known cause for blood loss such as recent surgery, trauma, or overt gastrointestinal haemorrhage; were premenopausal women; had an established reason for anaemia such as renal failure requiring haemodialysis or a haemoglobinopathy; or had been fully assessed recently for iron deficiency anaemia.

Iron state was assessed by measuring serum iron concentration, transferrin saturation, and serum ferritin concentration. Bone marrow aspiration for assessment of iron stores by Prussian blue staining was performed when results of blood measurements were non-diagnostic. A patient was classified as iron deficient if one or more of the following criteria were fulfilled: transferrin saturation <5%; serum ferritin concentration <30 µg/l (men) or <20 µg/l (women); bone marrow iron stores absent or notably reduced; haemoglobin concentration and mean corpuscular volume returned to normal after iron treatment (in two patients).

A clinical history including documentation of non-steroidal anti-inflammatory drugs ingested and dietary iron intake (by a dietitian) was obtained and a physical examination carried out for all patients with established iron

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deficiency. Gastrointestinal symptoms were grouped into the following categories: (1) upper gastrointestinal symptoms (dysphagia, heartburn, nausea, vomiting, and upper abdominal pain that was related to food or relieved by antacids); and (2) colonic symptoms (altered bowel habit, diarrhoea, constipation, rectal bleeding, and lower abdominal pain that was colicky or associated with altered bowel habit or relieved by the passage of stool or flatus).

All iron deficient patients underwent upper gastrointestinal endoscopy, and biopsy of the small bowel was performed in 67 patients. Colonic investigation was carried out in 90 patients. Colonoscopy was carried out in 67 patients and air contrast barium enema combined with flexible sigmoidoscopy in 53 (both examinations were done in 30 patients). Colonic investigation was not performed in 10 patients: five of these had upper gastrointestinal malignancy, and in five cases either the patient or the physician refused permission. Radiography of the small bowel was performed only when clinically indicated (13 patients).

Follow up data were obtained for all patients for whom the gastrointestinal investigations yielded normal results and for those patients who did not undergo colonic assessment. Patients found to be iron replete were not subjected to the same intensive gastrointestinal investigations.

Results

Altogether 365 patients were found to have microcytic anaemia: 232 were excluded for any of the above reasons and 33 had normal or raised iron stores, leaving 100 who fulfilled the criteria for iron deficiency. The male to female ratio for the 100 patients deficient in iron was 2.2:1 and their mean age 70.1 (SD 9.3) years. These figures were not significantly different from those for the iron replete group and reflected the elderly male population of this hospital. Both the mean haemoglobin concentration and the mean corpuscular volume were significantly lower in the iron deficient group compared with the iron replete group (table I).

TABLE I—Comparison of iron deficient and iron replete groups

	Iron deficient	Iron replete	p
Men: women	2:2	2:7	NS
Mean (SD) age	70.1 (9.3)	66.7 (10.5)	NS
Mean (SD) haemoglobin (g/l)	84 (18)	97 (11)	<0.001
Mean (SD) corpuscular volume (fl)	71.5 (6.4)	76.1 (4.1)	<0.001

Of 133 patients with microcytic anaemia, 50 had a haemoglobin concentration of 85 g/l or less and 44 of these were iron deficient. Six iron replete patients had haemoglobin concentrations of 85 g/l or less. Two had chronic renal failure and died within a year, and the remaining four had a gastrointestinal source of potential blood loss: one had gastric carcinoma; one had colonic cancer; one with metastatic prostatic cancer had a caecal angiodysplasia; and one with rheumatoid arthritis was taking high doses of aspirin.

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Table II shows the findings in the 100 patients deficient in iron. In 14 patients no cause for iron deficiency could be established. Benign, ulcerative gastrointestinal lesions (ulcerative oesophagitis, gastroduodenal mucosal erosions, gastric and duodenal ulcers) were the most common finding in these patients, being present in 36, of whom 19 took non-steroidal anti-inflammatory drugs regularly. Six patients had a chronic gastric ulcer and one a duodenal ulcer. Fourteen patients had ulcerative oesophagitis, of whom three had colonic neoplastic lesions (two cancers and one adenomatous polyp larger than 10 mm). Gastric or duodenal erosions were found in 14 patients, nine of whom were taking non-steroidal anti-inflammatory drugs and five had colonic disease (one cancer, three polyps, and one angiodysplasia).

TABLE II—Lesions associated with iron deficiency (n=100)*

Ulcerative oesophagogastrroduodenal lesions (n=36):	Colorectal neoplasia (n=20):	
Ulcerative oesophagitis	Cancer	14
Gastric or duodenal erosions	Adenomas (>10 mm)	6
Chronic gastric ulcer	Other colonic	
Chronic duodenal ulcer	conditions (n=3):	
Stomal ulcer	Angiodysplasia	2
Malignant oesophagogastric	Ulcerative colitis	1
pathology (n=6):	Small bowel lesions	
Oesophageal cancer	(Crohn's disease)	2
Gastric cancer	Dietary insufficiency	12
Other oesophagogastric conditions (n=25):	Use of non-steroidal	
Hiatus hernia (>10 cm)	anti-inflammatory drugs	31
Oesophageal varices	Miscellaneous	2
Angiodysplasia	Hereditary haemorrhagic	
After gastric surgery	telangiectasia	1
	Paroxysmal nocturnal	
	haemoglobinuria	1
	No cause found	14

*Total number of diagnoses exceeds 100 as 42 patients had several lesions.

Gastric surgery for peptic ulcers had been performed in 10 patients a mean of 15.3 (range 3-35) years earlier. Three patients had undergone Billroth I and three Billroth II gastrectomies and four had undergone vagotomy and drainage procedures; only one patient had stomal ulceration. A hiatus hernia was diagnosed endoscopically if at least 10 cm of stomach was visualised above the diaphragmatic hiatus. Among seven patients with a hiatus hernia five had another potential cause of iron deficiency—namely, gastric angiodysplasia (one), gastric ulcer (one), ulcerative oesophagitis and dietary insufficiency (one), and use of non-steroidal anti-inflammatory drugs (two). Malignant upper gastrointestinal lesions were found in six patients. Only one patient had oesophageal cancer and complained of mild heartburn without dysphagia. All five patients with gastric cancer had vomiting, pain, and weight loss on presentation. Dietary intake or iron was thought to be inadequate in 12 patients and the sole or major factor in five of these.

Upper gastrointestinal lesions were found in 60 patients and colonic lesions in 23. When the six patients with upper gastrointestinal malignancy and the 10 patients who had undergone gastrectomy were excluded, 7 (16%) of 44 patients with benign upper gastrointestinal lesions had coincidental colonic lesions (three colonic cancers and four adenomatous polyps greater than 10 mm in diameter) (table III). Three patients who were taking non-steroidal anti-inflammatory drugs either showed normal results on upper gastrointestinal endoscopy (two) or had mild oesophagitis (one), but despite the absence of colonic symptoms abnormalities were diagnosed by colonic assessment (two colorectal cancers and one caecal angiodysplasia).

Of 23 patients with colonic lesions, 14 had a total of 15 cancers; six had a total of 22 adenomatous polyps larger than 10 mm; two patients had caecal angiodysplasia; and one patient had ulcerative colitis. Seven colonic cancers were right sided. Two were Dukes's stage A, five stage B, and eight stage C. Eight patients with colorectal cancer had no specific colonic symptoms, and

TABLE III—Coincidental upper and lower gastrointestinal lesions in patients with iron deficiency (n=7)

Lesion	Site	Colonic symptoms	Coincidental upper gastrointestinal lesion
Cancer (Dukes's B)	Ascending colon		Erosions
Cancer (Dukes's B)	Ascending colon	Bleeding	Ulcerative oesophagitis
Cancer (Dukes's C)	Sigmoid (30 cm)	Bleeding	Ulcerative oesophagitis
Polyps* (two)	Sigmoid (50 cm)		Ulcerative oesophagitis
Polyp (one)	Sigmoid (25 cm)		Erosions
Polyp (one)	Transverse colon	Bleeding	Erosions
Polyps (11)	Caecum to rectum		Erosions

*All polyps were proved adenomas >10 mm in diameter.

TABLE IV—Correlation of intake of non-steroidal anti-inflammatory drugs (NSAIDs) with upper gastrointestinal symptoms and ulcerative gastroduodenal lesions

	Patients taking NSAIDs	Patients not taking NSAIDs	p
Upper gastrointestinal symptoms	18/31 (58%)	19/69 (28%)	0.01
Ulcerative gastroduodenal lesions*	12/27 (44%)	10/59 (17%)	0.02

*Ulcerative oesophagitis excluded.

TABLE V—Correlation of upper gastrointestinal symptoms with disease (n=90)*

Upper gastrointestinal symptoms	Upper gastrointestinal disease	
	Present	Absent
Present	31	5
Absent	23	31

*Ten patients who had undergone gastric surgery were excluded. Sensitivity=57 (SE 6.6%, specificity=86 (5.8%); positive predictive value=86 (5.7%); negative predictive value=57 (6.7%).

TABLE VI—Correlation of colonic symptoms with disease (n=90)

Colonic symptoms	Colonic disease	
	Present	Absent
Present	11	12
Absent	16	51

Sensitivity=41 (SE 9.5%, specificity=81 (4.9%); positive predictive value=48 (10.4%); negative predictive value=76 (10.7%).

three had upper gastrointestinal symptoms. Only one of the six patients with adenomatous polyps larger than 10 mm had noticed bleeding. Of 20 patients with colorectal cancer or adenoma greater than 10 mm, seven had acute ulcerative lesions on upper gastrointestinal endoscopy and four were taking non-steroidal anti-inflammatory drugs.

Non-steroidal anti-inflammatory drugs were used daily by 31 patients. In all but three dietary insufficiency or a specific gastrointestinal lesion accounted for the iron deficiency. The prevalence of upper gastrointestinal symptoms was significantly greater in patients taking non-steroidal anti-inflammatory drugs (table IV). Nineteen of these patients had causes for iron deficiency other than ulcerative gastroduodenal lesions; these included three colorectal cancers, one adenomatous colonic polyp, and one caecal angiodysplasia.

Lesions of the small bowel were an uncommon cause of iron deficiency in this series. No patient was diagnosed as having coeliac disease. Two patients had Crohn's disease of the small intestine, which was suspected in both on clinical grounds.

Gastrointestinal symptoms were correlated with endoscopic findings to determine whether symptoms correctly indicated the need for upper gastrointestinal endoscopy or colonic assessment. When the 10 patients who had undergone gastric surgery were excluded 44 of the remaining 90 iron deficient patients had no symptoms or physical signs to suggest a gastrointestinal lesion, but in 28 of these a gastrointestinal source of blood loss was shown. In 19 of these patients without gastrointestinal symptoms an upper gastrointestinal lesion was diagnosed, and in 12 a colorectal abnormality was found, including five colorectal cancers and four adenomatous polyps.

When patients who had undergone gastrectomy were excluded 23 (43%) of 54 patients without upper gastrointestinal symptoms had upper gastrointestinal lesions, whereas only 5 (14%) of 36 patients with no upper gastrointestinal lesions had symptoms (table V). Of 67 patients with no colonic symptoms, 16 (24%) had colonic lesions, which included eight colorectal cancers (table VI). In patients deficient in iron the positive predictive value of upper gastrointestinal symptoms for upper gastrointestinal lesions was 86% and the positive predictive value of colonic symptoms for colonic lesions was 48%.

Follow up information

The five patients who did not undergo colonic investigation were followed up for 13.8 (SD 5.4) months. One had persistent anaemia associated with a gastric ulcer that did not respond to treatment; he subsequently underwent

surgery. In the four other patients no gastrointestinal, or other, cause of anaemia was shown on recent examination (April 1985).

Of 21 patients with normal results of investigations of the upper and lower gut, 20 were followed up for up to 20 months and one was lost to follow up. Three died (at 0, 10, and 15 months) with no new diagnoses made either clinically or post mortem (in two). The remaining 17 were followed up for two to 20 months (mean 11.3 (SD 6.1)). In two transitional cell carcinoma of the bladder was diagnosed, and a further patient presented with overt gastrointestinal haemorrhage due to gastric erosions associated with non-steroidal anti-inflammatory drugs. The 14 remaining patients were well when last reviewed.

TABLE VII—Causes of anaemia in iron replete group (n=33)

Malignancy (n=8):		Non-malignant gastro-intestinal disease (n=2):	
Oesophageal or gastric	3	Gastric ulcer	1
Colonic	1	Angiodysplasia	1
Other	4	Chronic renal failure	4
Chronic inflammatory disease (n=16):		Others (n=5):	
Rheumatoid arthritis	9	Cardiomyopathy	2
Sepsis	6	Hyperparathyroidism	1
Pericarditis	1	Malnutrition	1
		Allergic bronchopulmonary aspergillosis	1

There were eight patients in the iron replete group with malignancy, four of whom had gastrointestinal malignancy (table VII). Although thorough gastrointestinal investigation was not done routinely in this group, 23 were followed up for two to 14 months. Eleven died; necropsies were conducted in all cases except for one patient with cancer of the oesophagus, and no new gastrointestinal lesion was diagnosed.

Discussion

Although 365 consecutive patients had microcytic anaemia, most (232) were excluded from the study. We considered thorough gastrointestinal investigation of these patients to be neither clinically relevant nor ethically justifiable. We investigated patients with microcytic anaemia in hospital in whom there was no known cause of iron deficiency anaemia.

In 1965 Beveridge *et al* reported gastrointestinal neoplasms in only 2% of iron deficient patients.³ The average age of their patients, however, was 45, and most were premenopausal women. Furthermore, the widespread use of upper and lower gastrointestinal fibreoptic endoscopy accounts for improved diagnosis of ulcerative oesophagitis, gastroduodenal ulceration, mucosal erosions, and gastrointestinal angiodysplasia. Dietary insufficiency of iron causing anaemia seems to be less prevalent nowadays.^{3,4}

A potential cause for iron deficiency was identified in 86 of our 100 patients, and a specific gastrointestinal condition (previous gastric surgery excluded) capable of causing blood loss was identified in 70. Benign ulcerative oesophagogastrroduodenal lesions are a common finding in iron deficiency anaemia. Two previous studies found these lesions in 45% and 57% of iron deficient patients.^{3,4} Here they were present in 36% of patients, and a further 24% had other abnormalities capable of causing chronic blood loss on upper gastrointestinal endoscopy. Thorough investigation of the large intestine as well as the upper gastrointestinal tract was planned in all patients to determine the need for colonic assessment in patients with a benign upper gastrointestinal lesion. When patients with oesophageal or gastric cancer and patients with previous gastric surgery were excluded 7 (16%) of 44 patients with a benign upper gastrointestinal lesion had coincidental colonic neoplasms including three cancers and four adenomatous polyps (10 mm or greater in diameter).

Use of non-steroidal anti-inflammatory drugs has often been implicated in unexplained iron deficiency anaemia.^{4,6} Three of 31 patients taking non-steroidal anti-inflammatory drugs (two with normal results of upper gastrointestinal endoscopy, one with mild oesophagitis) had colonic lesions (two colorectal cancers and one caecal angiodysplasia).

We emphasise the need for full colonic assessment in patients

deficient in iron with or without a benign upper gastrointestinal lesion on endoscopy, and even in patients with gastroduodenal mucosal ulceration related to non-steroidal anti-inflammatory drugs. This supports the opinion expressed by Fagan, who found that 10 of 96 cancers of the right side of the colon were initially misdiagnosed as an upper gastrointestinal lesion on the basis of a positive finding on barium meal examination.⁸ Most patients with colonic cancer were asymptomatic. Furthermore, colonic symptoms in anaemic patients were poor predictors of the presence of colonic cancers. Because this population studied comprised elderly, predominantly male, hospital inpatients the conclusions may not be applicable to a younger population of outpatients.

Gastric surgery is a well recognised cause of iron deficiency and results in the condition in 20-40% of patients.⁹⁻¹¹ Most studies suggest that its mechanism, although not established, is inadequate intake and malabsorption of food iron.^{9,12,13} Only one patient had a chronic duodenal ulcer, which is at variance with the findings of a similar prospective study in which pyloroduodenal ulceration was present in 19% of patients.⁴ Colonic assessment was not routinely performed in that series, and follow up data were not given. In the absence of overt gastrointestinal bleeding duodenal ulceration is a rare cause of iron deficiency. An association between a large hiatus hernia (intrathoracic stomach) and iron deficiency has been recognised for many years with gastrointestinal blood loss as the cause.¹⁴⁻¹⁶ Although seven patients had a large hiatus hernia, this was the sole cause for blood loss in only two.

Non-steroidal anti-inflammatory drugs were regularly used by 31% of the patients deficient in iron, a proportion no greater than that of apparently well men of a similar age taking such drugs.¹⁷ Upper gastrointestinal symptoms and ulcerative gastroduodenal lesions correlated strongly with use of non-steroidal anti-inflammatory drugs, being present in 58% and 44% of users respectively.

We confirm the findings of others that most patients deficient in iron have no history or physical signs suggestive of a gastrointestinal lesion.^{3,4} Altogether 49% of patients had no relevant symptoms or physical signs, yet in 64% of these a gastrointestinal source of blood loss was found and in 27% colorectal neoplasia was the cause of iron deficiency. When symptoms were present those relating to the upper gastrointestinal tract correlated well with the finding of upper gastrointestinal lesions though colonic symptoms correlated poorly with colonic lesions. Hence in patients with a proved benign upper gastrointestinal source of blood loss the absence of colonic symptoms does not obviate the need for full colonic assessment.

In conclusion, colonic assessment is necessary in elderly patients with microcytic iron deficiency anaemia and a benign lesion on upper gastrointestinal endoscopy. This should be carried out regardless of the use of non-steroidal anti-inflammatory drugs or lack of colonic symptoms.

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