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Original Article

Prevalence of Significant Endoscopic and Histopathologic Findings in Patients Presenting with Unexplained Iron Deficiency Anemia

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Abstract

Background: In practice, however, not all anaemic patients undergo appropriate diagnostic tests for the detection of iron deficiency anaemia (IDA), and a significant portion of patients with IDA do not receive endoscopic evaluations. Accordingly, this study aimed to detect the prevalence of significant endoscopic (upper and lower endoscopy) and pathological findings in patients presenting with unexplained iron deficiency anaemia.

Methods: One hundred twenty-four patients with confirmed IDA with no obvious cause who visited the Internal Medicine Clinic were randomly selected. Patients with active bleeding, pregnant or lactating females, or those with contraindications to sedation were excluded. Upper and lower endoscopy were held in the endoscopy unit of Specialized Medical Hospital and tissue biopsy from significant endoscopic findings was sent for histopathological examination.

Results Our study showed that **86.3**% of participants displayed positive findings. main causes of iron deficiency anemia in the included 124 patients based on the upper and lower GIT endoscopic and pathological findings were gastritis and duodenitis (17.7%) followed by chronic nonspecific colitis (11.3%) followed by infectious colitis and hemorrhoids (10.5%) then GI malignancies (gastric and colonic) (9.6%) then Ulcerative colitis (8.9%) and Celiac disease (6.5%).

Conclusion: Upper and lower endoscopy is an important procedure for the evaluation of patients with unexplained IDA and for the early detection of silent gastrointestinal malignancies.

Keywords: Iron Deficiency Anemia; Upper Endoscopy; Lower Endoscopy.

INTRODUCTION

Iron deficiency Anaemia is often silent and chronic; it may go untreated entirely. Nonspecific symptoms such as weakness, exhaustion, difficulty concentrating, and low productivity at work are attributed to reduced iron-containing enzyme activity and insufficient oxygen transport to body tissues. It varies to what degree these non-hematologic consequences of an iron shortage show up prior to the development of anaemia. A tissue iron shortage exhibits modest symptoms that may not improve with iron treatment. Iron deficiency has been linked to delayed mental and motor development as well as decreased cognitive function in children, and it's unclear if short-term treatment has an impact on these effects [1].

Up to one-third of patients with iron deficiency anemia (IDA) show significant GI lesions, as identified by colonoscopy and EGD, with 10 to 15% of these patients presenting malignancies. Approximately one-third of individuals exhibiting anemia also have iron deficits. Moreover, a significant fraction of IDA patients does not get an endoscopic assessment [2].

If there is no visible cause of bleeding in postmenopausal women or men with IDA, GI tract blood loss is assumed to be the cause. Consequently, GI endoscopy has been the standard of care in the community to rule out GI pathology. The primary health care recommendations of the World Health Organization do not currently include the screening of anemia and iron deficiency in premenopausal women who are not pregnant [3].

GI disorders can be broadly classified into four groups based on the size of the lesion: precancerous lesion, early GI cancer, advanced GI cancer, and benign GI diseases.In the medium term, benign gastrointestinal conditions like ulcers, gastritis, and bleeding will not progress into malignancies. If precancerous GI lesions are not identified and treated in a timely manner, they may progress into early or even advanced GI cancer [4].

METHODS

This is an open-label prospective study conducted on one hundred twenty-four patients with IDA who attended the endoscopy unit of the specialised medical hospital at Mansoura University. Patients with active bleeding, pregnant or lactating females, contraindications of sedation (uncontrolled diabetes mellitus, uncontrolled thyroid disorders, pregnancy, respiratory embarrassment) were excluded. Our ethical committee authorised the study protocol, and prior to the procedure, all subjects provided written consent.

Measures:

All patients underwent a complete blood count (CBC) with detection of specific hematological parameters. Serum ferritin, iron and total iron binding capacity, INR, serum albumin and bilirubin levels, ALT (Alanine Amino-transferase), AST (Aspartate Aminotransferase), ESR, serum creatinine, occult blood in stool (FOBT kits) A small sample of stool collected in a clean container is usually taken on consecutive days with precaution before testing, including stopping non-steroidal anti-inflammatory drugs, vitamin C tablets, raw vegetables and fruits, and red meat often 48 to 72 hours before the test as they give a false positive [5]. Using immunochemical assay which detect globin chain of hemoglobin [6].

All those proved with unexplained iron deficiency anemia were prepared to perform upper endoscopy and colonoscopy in later appointment.

Procedures

Esophgogastroduodenoscopy and colonscopy were performed in our endoscopy unit by the same endoscopist under conscious sedation, Endoscopic examination was done by (PENTAX medical EPK-I 5000, Tokyo, Japan). We usually started with colonscopic examintion. Complete ileo-colonscopy was done to all patients then esohgeo-gastroduoenoscopy , any macroscopic lesion was detedcted ,documented and tissue biopsy was taken and sent for histopathological examination by the same pathologist.

Statistical analysis

The IBM computer performed the following data analysis using SPSS (version 15): quantitative variables shown as range, mean, and standard deviation; qualitative variables presented as percentage and quantity; When comparing two groups for a quantitative variable in parametric data (SD < 25% mean), the unpaired t test was employed. For non-parametric data (SD > 50% mean), two groups were compared using the Mann-Whitney-Wilcoxon test. Data measured more than once for the same subjects were analysed using repeated measures ANOVA.

Sample size was calculated by the following formula (Daniel and Cross, 2013):Z = Z statistic for the level of confidence = 1.282 for 80% confidence level.P = Expected prevalence = 0.75. Based on previous research [7], the prevalence of GI lesions detected by upper and lower GI endoscopies is expected to be 75% in IDA patients.d = Allowable (Acceptable) margin of error = ± 5% since P falls in the range of 0.1 to 0.9 (d= 0.05).A total sample size of 124 IDA patients achieves an 80% confidence level for expected prevalence of 75% and an acceptable margin of error of ± 5%.

RESULTS

The present study included 124 iron deficiency anemia patients, 55 males and 69 females, with a mean age of 44.9 ± 15 years and female predominance (55.6%). who visited our specialized medical hospital between April 2022 and December 2023. All patients underwent upper and lower GIT endoscopy; no abnormalities were present in 13.7% of patients; upper GIT abnormalities were present in 23.4% of patients; lower GIT abnormalities were present in 33.1% of patients. Abnormalities in both upper and lower GIT endoscopy were present in 29.8% of patients, as shown in Table (1).

Upper Endoscopy Results:

The commonest finding in the upper GI endoscopy was gastritis (12.1%). Gastroesophageal reflux disease (GERD) was diagnosed in 8.1% of patients, which was the second most common finding. Peptic ulcers and atrophic mucosa were present in 5.6% and 4.8% of patients, respectively. Mass was diagnosed in 5.6% of patients. Four patients with mass were diagnosed with cancer of the of the stomach later by biopsy, and three cases were diagnosed as benign polyps. Esophageal varices were present in 4.8% of patients (2.4% in grades 1 and 2.4% in grades 2). The mosaic appearance of the duodenum was shown in 3 patients (2.4%), who were later diagnosed with celiac disease, as shown in Table (2).

Lower Endoscopy results:

Lower GIT endoscopy results showed that the colon was the commonest affected site (26.6%) followed by cecum (25%). Anorectum and terminal ileum both were affected in (4.85%) of patients and sigmoid colon was affected in (1.6%) of patients. The commonest findings in lower GIT endoscopy were hyperemia and edema (16.1%), ulcers in colon and terminal ileum (8%) and polyps with villous hypertrophy (14.55%). Findings of lower frequencies were diverticula, mass, stunted villi, or nodular mucosa in 6.55% of patients. Vascular lesions were present in 1.6% of patients as shown in Table (3).

Pathological findings in upper Endoscopy:

About 53.7% of upper endoscopy biopsies revealed normal findings. About 25% of patients showed active inflammatory cells, suggesting gastritis or duodenitis. While 6.5% of pathology results revealed the presence of chronic inflammatory cells and fibrinoid necrosis of ulcers, 4 cases (3.2%) showed the presence of gastric carcinoma and 3 (2.4%) benign polyps. Six cases (5.6%) showed the presence of atrophic mucosa. Three cases were diagnosed as celiac disease (2.7%), as shown in Table (4).

Pathological findings in Lower Endoscopy:

Lower GIT pathology was normal in 37% of patients. Inflammatory cells were present in 35.5% of patients. Inflammatory cells were present in the colon (colitis) in 30.7% of patients and in the ileum (enteritis) in 4.8% of patients. Ulceration was present in 4.03% of patients. Dysplasia was present in 9.7% of patients. Adenoma and hypertrophied villi were present in 7.3% of patients. Atrophic villi were present in 6.5% of patients. Adenocarcinoma was present in 4.8% of patients, and signet ring carcinoma was present in 1.6% of patients. The final diagnosis was made according to lower GIT endoscopic and pathological findings, which revealed that 37% of patients did not have lower GIT disease. The commonest lower GIT disease was chronic non-specific colitis (11.3%), followed by infectious colitis (10.5%), and hemorrhoids (8%). Ulcerative colitis was diagnosed in 8.9% of patients, adenoma was diagnosed in 7.3%, and malignancy was present in 6.5% of patients. Crohn's disease was diagnosed in 5.6% of patients. Vascular lesions were present in 1.6% of patients, and diverticular disease was present in 2.4% of patients, as shown in table (5). Final diagnosis and main causes of iron deficiency anemia in the included 124 patients based on the upper and lower GIT endoscopic and pathological findings: revealed that most common cause is gastritis and duodenitis (17.7 %) followed by chronic nonspecific colitis (11.3 %) followed by infectious colitis and hemorrhoids (10.5%) then Malignancy (gastric and colonic) 9.6 % then Ulcerative colitis (8.9%) and Celiac disease (6.5 %) as shown in table (6).

Fecal occult blood test:

Faecal occult blood had the ability to detect the presence of GIT disease in 107 patients out of 124 patients, showing 82.6% sensitivity and a positive predictive value of 100%. However, specificity and negative predictive value could not be assessed as no true negative cases were found by endoscopy and/or pathology; hence, there were no false positive cases as shown in table (7).

Comparison between normal and abnormal patients:

The included patients were divided into 2 groups according to the presence of abnormal endoscopic findings (either upper or lower): the normal endoscopy group included 22 patients, and the abnormal endoscopy group included 102 patients. The mean age of patients in the abnormal endoscopy group was higher than that in the that in the normal endoscopy group ($p = 0.02$). There were no statistically significant differences between both groups regarding sex, body mass index, or smoking rate. There were no statistically significant differences between normal and abnormal endoscopy groups regarding the to the incidence of hypertension, diabetes, thyroid disease, and cardiovascular disease. There were no statistically significant differences between normal and abnormal endoscopy groups regarding haemoglobin, MCV, MCH, ferritin, TIBC, and ESR. However, serum iron was lower in the abnormal endoscopy group than in the in the normal endoscopy group, with a statistically significant difference ($p = 0.03$). There were no statistically significant differences between both normal and abnormal endoscopy groups regarding renal and liver function tests.

The abnormal study group was subdivided into an upper endoscopy abnormal group, a lower endoscopy abnormal group, and both an upper and lower abnormal group. There were no statistically significant differences between the studied groups regarding associated medical disorders, except that cardiac diseases were more frequent among the upper and lower abnormalities groups with statistically significant differences ($p = 0.03$). Serum iron had the lowest mean values among the upper GIT endoscopic abnormalities group, with statistically significant differences ($p = 0.016$).

Table (1) : Abnormal findings in both upper and lower GIT endoscopies

	Total cohort (n= 124 patients) No. (%)
Upper Endoscopy	29 (23.4%)
Lower Endoscopy	41 (33.1%)
Both upper and lower Endoscopy	37 (29.8%)
No abnormalities	17 (13.7%)

Table (2): Upper endoscopy results

	Total cohort (n= 124 patients) No. (%)
No abnormality	58 (46.9%)
Inflammation:	
- Gastritis	15 (12.1%)
- Duodenitis	4 (3.2%)
- Gastritis and duodenitis	8 (6.5%)
Gastroesophageal reflux	10 (8.1%)
Ulcers:	7 (5.6%)
- Gastric ulcer	5 (4%)
- Duodenal ulcer	1 (0.8%)
- Gastric and duodenal ulcer	1 (0.8%)
Atrophic mucosa	6 (4.8%)
Mass	7 (5.6%)
- cancer stomach	4 (3.2%)
- Benign polyps	3 (2.4%)
Esophageal varices	6 (4.8%)
Grade of varices	
- Grade 1	3 (2.4%)
- Grade 2	3 (2.4%)
Mosaic duodenum (celiac disease)	3 (2.4%)

Table (3): Lower endoscopy results

	Total cohort (n= 124 patients) No. (%)
No abnormalities	46 (37.1%)
Site of lesions:	
- **Colon**	33 (26.6%)
- **Cecum**	31 (25%)
- **Anorectum**	6 (4.85%)
- **Sigmoid**	2 (1.6%)
- **Terminal ileum**	6 (4.85%)
Hyperemia and edema	20 (16.1%)
Hemorrhoids	10 (8%)
Diverticula	3 (2.4%)
Ulcers	9 (7.25%)
Polyps	18 (14.55%)
Mass	8 (6.55%)
Stunted villi or nodular mucosa	8 (6.55%)
Vascular lesions as telangiectasia	2 (1.6%)

Table (4): Upper endoscopy pathology results

	Total cohort (n= 124 patients) No. (%)
Normal findings	58 (53.7%)
- Active Inflammatory cells suggesting gastritis or duodenitis	27 (25%)
- Chronic inflammatory cells + Fibrinoid necrosis	7 (6.5%)
- Total	34 (31.5%)
Mass	7 (6.5%)
Gastric carcinoma	4(3.2%)
Benign polyps	3(2.4)
Atrophic mucosa	6 (5.6%)
Celiac disease	3 (2.7)

Table (5): Lower GIT pathological findings and final lower GIT diagnosis according to pathological and endoscopic findings

	Total cohort (n= 124 patients) No. (%)
Normal finding	46 (37%)
Inflammatory cells	44 (35.5%)
Enteritis	6 (4.8%)
Colitis	38 (30.7%)
Ulceration	5 (4.03%)
Dysplasia	12 (9.67%)
Adenoma	9 (7.3%)
Carcinoma	8 (6.5%)
- **Adenocarcinoma**	6 (4.8%)
- **Signet ring carcinoma**	2 (1.6%)
Final diagnosis of lower GIT lesions	
- **Normal findings**	46 (37%)
- **Crohn's disease**	8 (6.5%)
- **Ulcerative colitis**	11 (8.9%)
- **Chronic non- specific colitis**	14 (11.3%)
- **Infectious colitis**	13 (10.5%)
- **Malignancy**	8 (6.5%)
- **Hemorrhoids**	10 (8%)
- **Vascular lesions or telangiectasia**	2 (1.6%)
- **Diverticular disease**	3 (2.4%)
- **Adenoma**	9 (7.3%)

Table (6): Final diagnosis

		Total cohort (n= 124) No. (%)
Gastritis and/ or duodenitis		22 (17.7%)
Peptic Ulcer		7 (5.6%)
Esophageal varices		6 (4.8%)
Crohn's disease		7 (5.6%)
Ulcerative colitis		11 (8.9%)
Chronic non- specific colitis		14 (11.3%)
Infectious colitis		13 (10.5%)
Celiac disease		8 (6.5%)
Malignancy	Total	12(9.6%)
	Cancer stomach	4 (3.2%)
	Colon adenocarcinoma	6 (4.8%)
	Signet ring carcinoma	2 (1.6%)
Hemorrhoids		13 (10.5%)
Vascular lesions or telangiectasia		5 (4.1%)
Diverticular disease		6 (4.8%)

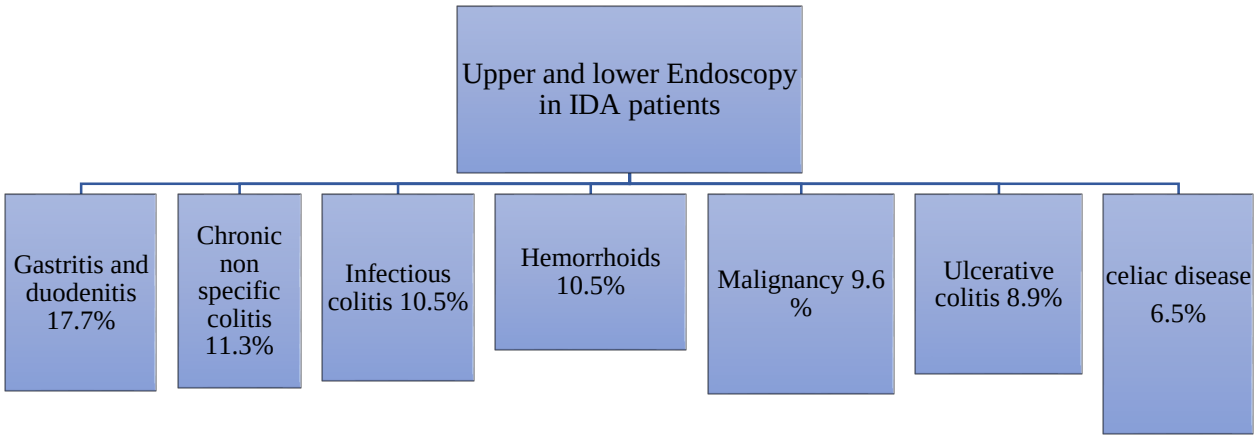

Figure (1): Flow chart describing the important findings detected by upper and lower endoscopy

DISCUSSION

Due to hidden GI blood loss, iron deficiency anaemia (IDA) is typically not detected until the patient exhibits symptoms. Even though GI lesions were found in symptomatic patients more frequently, asymptomatic IDA patients may potentially have significant GI abnormalities unrelated to the nonspecific symptoms of the disease [8,9].

The patient populations in a number of earlier studies, including the one by Annibale *et al.* [9], which reported GI endoscopic results in 581 asymptomatic women and 87 males with IDA, were disproportionately gendered. Previous research has indicated a preponderance of females, with a male-to-female ratio of 1:1.6 [10-12], as our study, which included 124 iron deficiency anaemia patients, 55 male and 69 female, with a mean age of 44.9 ± 15 years and female predominance (55.6%).

Kim *et al.* assessed the GI endoscopic results of young males exclusively, and they recommend endoscopy for young men with IDA who are asymptomatic [13] .According to Todd et al., GI referral is not necessary for asymptomatic women with IDA under 50 years of age unless their condition does not improve with treatment for other known reasons and appropriate iron supplementation [14].

Despite the rarity of atrophic gastritis (AG) as the cause of IDA, AG has been identified in numerous investigations as a major GI lesion in IDA patients [8,15]. The hypochlorhydria that may be associated with AG may hinder or impede the absorption of iron. In this study, This percentage is consistent with the findings of multiple other studies, including those on duodenitis and gastritis (17.7%) [15]. The proportion of AG patients in this study was higher than that of Niv *et al.* (14.5%) [8] and less than that reported by Marignani *et al.* (50%) [16].

Since peptic ulcers typically manifest as bleeding, we were unable to confirm the strong correlation found by Kim et al. /13/between the severity of IDA and the existence of peptic ulcers [10], causing the low percentage (peptic ulcer 5.6%).

Celiac Disease (CD) in IDA patients without symptoms is referred to as "silent" or "atypical." In our study A higher percentage of 6.5% than in previous research (2.9% to 6%) developed CD among EGD patients [14,17,18].

The classic presentation of malabsorption with diarrhoea, the absence of classical extra-intestinal features, subclinical or asymptomatic, more prevalent silent forms, and a possible disease marked by positive serology with a healthy intestinal mucosa on biopsy are all included in the broad clinical spectrum of CD [19].

Serologic testing advances have significantly altered the global epidemiology of CD by identifying higher rates of silent or atypical CD [20], which is linked to a lower quality of life and a higher death rate [21]. People who have asymptomatic CD do not exhibit the typical symptoms of CD, and they react differently to gluten removal than is typical. Frequently, these patients receive an unintentional diagnosis as a result of population screening or while using case-detection techniques on high-risk patients [19].

Additionally, they are identified during small bowel biopsies for additional studies, particularly in cases where IDA may suggest the existence of potential GI cancers. Insufficient assessment could result in needless delays in diagnosis [18].

Chronic IDA is frequently caused by gastrointestinal (GI) cancer [22], particularly when right-sided tumours are present. In older patients, neglecting to assess anaemia may result in a delayed diagnosis [23].

In Acher's study [24], out of 440 individuals with colorectal cancer, 166 (38%) had IDA at the time of diagnosis. In a different study, 32,390 patients with IDA /25/were found to be 24.0% male and 75.98% female. Within the observation period, 2051 patients diagnosed by cancer.

Our study showed prevalence of colonic adenocarcinoma (4.8%) and signet ring carcinoma (1.6%) in enrolled patients and 9.6%% involved all malignancies of GIT. It is imperative to look for GI cancers that may be asymptomatic when IDA is present. A 5.3% to 6.5% malignancy detection rate has been reported in previous investigations [17, 26].

Although Wilcox, Annibale, and Bini et al.'s widely recognised studies [9,10, 27] show malignancy detection rates ranging from 3% to 21%, they deemed these numbers to be non-representative.

According to other research, IDA patients who are asymptomatic are more likely to have GI malignancies, and they should be referred for GI assessment [28]. In elderly individuals with asymptomatic IDA, Niv et al. reported a high prevalence of colon cancers, primarily right-sided colon carcinoma [8].

Even though upper GI cancer will probably be an uncommon discovery, Van Mook et al. observed that EGD should always be performed in asymptomatic patients with IDA and negative colonoscopies, especially among older patients and NSAID users [11]. Dignass et al. discovered a strong relationship between intestinal neoplasia activity, severity, and blood loss volume [29].

As a possible aetiology of IDA, 13 patients (10.5% of all asymptomatic IDA patients) had non-bleeding haemorrhoids. According to **Park *et al.*** [15], 15.7% of patients with anaemia in young women do not have gastrointestinal symptoms and have non-bleeding haemorrhoids, which is consistent with our data.

After a colonoscopy, it was discovered that eighteen individuals had inflammatory bowel disease, seven individuals (5.6%) had Crohn's disease, and eleven individuals (8.9%) had ulcerative colitis. One important early sign of Crohn's disease may be IDA. When Annibale et al. thoroughly examined 71 IDA patients, they found one asymptomatic woman who had Crohn's disease [9].

Suspicions of latent inflammatory activity should be raised in individuals who experience a quick recurrence of IDA [29].

The most prevalent chronic bacterial infection in the world, Helicobacter pylori (H. pylori) is directly linked to the pathophysiology of peptic ulcer disease, gastric adenocarcinoma, and mucosa-associated lymphoid tissue lymphoma.

According **to Najafi *et al.*** [30], there may be a correlation between the prevalence of H. pylori infection and the incidence of stomach cancer.

According to Annibale *et al.* [9] 13 out of 71 IDA patients developed gastritis caused by H. pylori. Twenty-eight IDA patients (22.5%) in this study had H pylori of 49 patients with active inflammatory cells on pathological examination. Thus, in IDA patients, gastritis may be linked to stomach and colon malignancies.

The **strength** of this study is the large sample size and wide age spectrum of the investigation. Our mean age was 44.9 ± 15 years, while most previous studies involved older patients with a mean age ranging from 60 to 70 years [12]. Despite this strength, there are some limitations. First, we studied patients in one center. Second, the upper and lower endoscopy were not performed by the same endoscopist. Finally, the long-term follow-up was not included in our study.

Conclusion: Upper and lower endoscopy is an important and safe procedure and should be recommended for evaluation of patients with unexplained IDA and for early detection of silent gastrointestinal malignancies.

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Conflicts of Interest: There are no conflicts of interest

Ethics approval and consent to participate: The Ethics Review Board of Mansoura University's Faculty of Medicine approved the study methodology, and all subjects provided informed written consent in accordance with the Declaration of Helsinki. MS.22.05.2001 is the committee's reference number.

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