Upper and lower gastrointestinal endoscopy in patients with iron deficiency anemia

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SUMMARY
Introduction/Objective The most common cause of iron deficiency anemia (IDA) in both men and postmenopausal women are gastrointestinal diseases. This study aimed to determine the frequency of pathological and diagnostic findings observed on esophagogastroduodenoscopy (EGDS) and colonoscopy in IDA patients, and examine associations between demographic, anamnestic, and clinical features, with findings found on endoscopy.

Methods A retrospective cross section study of patients with IDA was conducted.

Results Eighty-five patients with IDA were included, mean age of 60.3 ± 18.8 years, with 51.8% being women. Esophagogastroduodenoscopy, colonoscopy, or both was performed in 96.5%, 71.8%, and 70.6% of patients, respectively. The cause of IDA was established in 65.9% of cases. Diagnostic findings were observed in those who underwent EGDS, colonoscopy, or both in 43.9%, 47.5%, and 15.9% of patients, respectively. Diagnostic findings on EGDS were significantly more common in patients older than 50 years then in younger patients (p = 0.031). Patients with a diagnostic finding on colonoscopy more commonly reported weight loss (p = 0.046) and change in bowel habit (p = 0.012), alongside positive fecal occult blood test (FOBT; p = 0.012); they rarely had anemia previously (p = 0.001), rarely used iron supplements (p = 0.022), and were more likely to have malignancy in their past medical history (p = 0.043).

Conclusion Diagnostic findings on EGDS were more commonly observed in older patients, while diagnostic findings on colonoscopy were more common in those with weight loss, change in bowel habit, positive FOBT, and prior malignancy. Colonoscopy was more often diagnostic in patients without anemia or iron supplementation in the past.

Keywords: anemia; endoscopy; neoplasm; angiodysplasia

INTRODUCTION

Iron deficiency anemia (IDA) is the most common type of anemia. It is estimated that its incidence in the general population is 12% and 23% in the population of hospitalized patients [1–4]. Approximately 1–5% of men, and 5–12% of women who are not pregnant have IDA [5, 6, 7]. In premenopausal women, the most common cause of IDA is menstrual bleeding, whereas in both men and postmenopausal women, the underlying cause is most often gastrointestinal blood loss [7, 8].

This study aimed to determine the frequency of pathological and diagnostic findings observed on esophagogastroduodenoscopy (EGDS) and colonoscopy in IDA patients, and examine associations between demographic, anamnestic and clinical features, with findings found on endoscopy.

METHODS

A retrospective cross section study was conducted for one year, from January 2014 to January 2015, at the Clinic for Gastroenterology and Hepatology, Clinical Center of Serbia. The inclusion criterion was IDA. Anemia was defined as a reduction in hemoglobin level below 130 g/L or hematocrit level below 0.40 for men, and hemoglobin level below 120 g/L or hematocrit level below 0.35 for women [2]. IDA was defined as an anemia with the following characteristics: reduced serum iron (men < 11 μmol/L; women < 7 μmol/L), decreased ferritin (men < 20 μg/L; women < 10 μg/L), transferrin saturation (< 15%), elevated total iron binding capacity (> 75.1 μmol/L), elevated transferrin receptor (> 1.76 mg/L) and/or reduced mean corpuscular volume (< 80 fl.). The exclusion criteria were the age < 18 years and the presence of another disease as the obvious cause of IDA. Patients with malignancy in the past medical history were only included if more than five years had passed since oncological treatment, and if they did not have a recurrence of the primary tumor.

A review of medical records was performed and the collected data included demographic, anamnestic and clinical data, as well as the results of endoscopic examination. Demographic data included sex and age. The anamnestic data included symptoms (including manifest bleeding), drug use, past medical history and comorbidities, and family history. Clinical data...
Statistics

Descriptive and analytical statistics were used. Continuous variables were described as the average value ± standard deviation, while frequency and proportions were utilized for discontinuous variables. The normality of the distribution for continuous variables was evaluated by the Kolmogorov–Smirnov test. Based on data from previous studies, the findings of milder forms of esophagitis, hiatus hernia, esophageal varices without red spots, mild forms of erosive gastritis and duodenitis, and the presence of smaller polyps were classified as pathological rather than diagnostic findings on EGDS [7, 8, 11].

The diagnostic finding category on colonoscopy included: neoplasms (colon or terminal ileum), one or more polyps with a diameter > 15 mm, active colonic ulceration > 10 mm, vascular ectasias, inflammatory bowel disease, post radiation colitis and active colitis [7, 9, 12]. The findings of uncomplicated colonic diverticulosis, non-bleeding hemorrhoids, and small colonic polyps were classified into the pathological finding group, and were not diagnostic [7, 8].

RESULTS

Demographic data

The study included 85 patients with IDA. The average age of the patients was 60.3 ± 18.8 years (range 18–87 years). Of the total number of subjects, 51.8% (n = 44) were women.

Anamnestic data

The most commonly reported general symptoms were malaise and/or fatigue, as well as weight loss. The gastrointestinal-specific symptoms were present in 65.9% (n = 56) of the patients, the most common of which being abdominal pain and change in bowel habit. An active episode of GIT bleeding was evidenced in one third of the cases and included hematemesis in 3.5% (n = 3), melena in 24.7% (n = 21), and rectorrhagia in 22.4% (n = 19) of the patients. Of the comorbid diseases, most patients had arterial hypertension (44.7%), followed by diabetes mellitus (14.1%) and cardiac arrhythmia (12.9%). Of the concurrent GIT diseases, the most common was dyspepsia. One half of the patients had a prior history of anemia, for a period for 2–180 months. Regarding prior medication use, most patients reported taking iron preparations. The anamnestic data of the patients is shown in Table 1.

| Symptom                          | Count (n) | Percentage |
|----------------------------------|-----------|------------|
| Malaise and/or fatigue           | 71        | 84.5       |
| Abdominal pain                   | 37        | 49.3       |
| Weight loss                      | 34        | 45.9       |
| Irregular bowel empting           | 32        | 38.8       |
| Overt gastrointestinal bleeding  | 33        | 39.6       |
| Dyspepsia                        | 16        | 23.9       |
| Heartburn                        | 12        | 17.6       |
| Tympanites                       | 10        | 12.9       |
| Vomiting                         | 9         | 12.9       |
| Loss of appetite                 | 4         | 5.8        |
| Syncope                          | 2         | 2.9        |
| Medication and alcohol consumption|          |            |
| Iron preparations                | 23        | 27.1       |
| Acetylsalicylic acid             | 19        | 22.4       |
| Anticoagulants                   | 14        | 16.5       |
| Nonsteroidal anti-inflammatory drugs| 10        | 11.8       |
| Anti-platelet drugs              | 7         | 8.2        |
| Alcohol consumption              | 4         | 4.7        |
| Comorbidities                    |           |            |
| Arterial hypertension            | 38        | 44.7       |
| Diabetes mellitus                | 12        | 14.1       |
| Arrhythmia                       | 11        | 12.9       |
| Cerebrovascular insult           | 8         | 9.4        |
| Chronic obstructive pulmonary disease| 3         | 3.5        |
| Past medical history             |           |            |
| Dyspepsia                        | 16        | 18.8       |
| Ulcer disease                    | 8         | 9.4        |
| Gastroesophageal reflux disease  | 3         | 3.5        |
| Overt gastrointestinal bleeding in past medical history| 38| 44.7|
| Malignancies                     | 6         | 7.1        |
| Anemia in past medical history   | 45        | 52.9       |
| Family history                   | 17        | 20         |
| Malignancies in family history   |           |            |
Clinical data

The majority of patients presented with abdominal tenderness and pallor. In a significantly lower percentage of patients, hepatomegaly, a palpable abdominal mass, and ascites were noted. None of the patients had splenomegaly. A pathological finding on digital rectal examination was present in slightly less than one half of the patients, with results of this examination not determined in 24.7% (n = 21) of the patients. A fecal occult blood test (FOBT) was performed in 56.5% (n = 48) of the patients, with a positive finding in 23.5% (n = 20) of the cases. The clinical data of the patients is shown in Table 2.

Table 2. The clinical data of the patients (n = 85*)

| Signs                                      | %    | n  |
|--------------------------------------------|------|----|
| Pallor                                     | 51.8 | 44 |
| Abdominal tenderness                       | 65.9 | 56 |
| Hepatomegaly                               | 7.1  | 6  |
| Abdominal mass                             | 3.5  | 3  |
| Ascites                                    | 2.4  | 2  |
| Pathological finding of digital rectal examination | 43.8 | 28 |
| Melena                                     | 34.3 | 22 |
| Rectorrhagia                               | 3.1  | 2  |
| Palpable mass of the rectum                | 3.1  | 2  |
| Palpable internal hemorrhoids              | 3.1  | 2  |

*For digital rectal examination n = 64

Endoscopy

EGDS was performed in 96.5% (n = 82) of the subjects, and colonoscopy in 71.8% (n = 61). Both procedures were performed in 70.6% (n = 60) of the patients. Using these modalities, the cause of IDA was established in 65.9% (n = 56) of the cases. A pathological finding on EGDS was present in 93.9% (n = 77) of those included in the study.

A diagnostic finding on EGDS was present in 43.9% (n = 36) of the patients. The highest percentage of patients had angiodysplasia of the stomach and/or duodenum, gastric ulcer, stomach neoplasm, and duodenal ulcer. Detailed data of the diagnostic and pathological findings of EGDS is shown in Table 3. The selected diagnostic findings of EGDS is shown in Figure 1.

Table 3. Pathological and diagnostic finding of esophagogastroduodenoscopy (n = 82)

| Finding                                     | %    | n  |
|---------------------------------------------|------|----|
| Gastroesophageal reflux disease*            | 8.5  | 7  |
| Esophageal varices                          | 1.2  | 1  |
| Hiatus hernia*                              | 6    | 5  |
| Chronic gastritis/gastroduodenitis**        | 37.8 | 31 |
| Gastric and/or duodenal angiodysplasia      | 14.6 | 12 |
| Gastric ulcer                               | 6    | 5  |
| Gastric neoplasm                            | 6    | 5  |
| Duodenal ulcer                              | 4.8  | 4  |
| Duodenal neoplasm                           | 1.2  | 1  |
| Polyps                                      | 2.4  | 2  |
| Mb. Crohn                                   | 2.4  | 2  |
| Gluten sensitive enteropathy                | 1.2  | 1  |
| Gastrointestinal stromal tumor              | 1.2  | 1  |

Bold – pathological and diagnostic finding;
*diagnostic finding in 2.4% (n = 2) of the patients;
**diagnostic finding in 10.9% (n = 9) of the patients

The pathological finding on colonoscopy was seen in 78.6% (n = 48) of the patients. 47.5% (n = 29) had a diagnostic finding. The most common were colonic neoplasms and inflammatory bowel disease. Diagnostic and pathological findings of colonoscopy are shown in Table 4.

In 15% (n = 9) of the patients, there was a positive finding on both EGDS and colonoscopy. The most common diagnostic finding in the upper and lower parts of the GIT is angiodysplasia, which was present in 4.7% (n = 4) patients.

Figure 1. The selected diagnostic finding of esophagogastroduodenoscopy; A) esophageal carcinoma; B) gastro-esophageal reflux disease with stenosis after extraction of the foreign body; C) esophageal varices; D) gastric lymphoma infiltration; E) gastric ulcer, Forrest Ib; F) and G) bleeding gastric ulcer, Forrest Ib, during hemostasis; H) two ulcers of the antral region
Factors associated with diagnostic finding on endoscopy

A positive diagnostic finding on EGDS was significantly more common in patients older than 50 years compared to younger patients. For other socio-demographic, anamnestic, and clinical data there was no significant difference (Table 4). Patients with diagnostic findings on colonoscopy more commonly reported symptoms of weight loss, and change in bowel habit; they rarely had anemia prior, and rarely used iron supplements, and often had malignancy in their past medical history. Patients with diagnostic findings on colonoscopy often have a positive FOBT. For other assessed variables, no significant difference was found (Table 5).

**DISCUSSION**

Gastroenterological and endoscopic examinations are a necessity in the workup of patients with IDA; in fact, 7.6% to 13% of patients are referred to the gastroenterologist because of IDA [13, 14].

In our study, the frequency of diagnostic findings on EGDS and colonoscopy was in line with previously published results, indicating that the incidence of positive endoscopic findings in IDA patients is in the range of 30–85% [8, 9, 15–19].

A high percentage of pathological findings but not diagnostic findings were observed for EGDS in our study, which can be explained by the subjective assessment of the endoscopist regarding the existence of gastritis/gastroduodenitis (the most common overall pathological finding). Another reason may be the fact that, in our study, we described uncomplicated hiatus hernia as a pathological finding. The impact of hiatus hernia on the development of IDA is a matter of some debate. In some studies, hiatus hernia was considered a normal finding [11]. The exception is a large hernia (hernia ≥ 4 cm, measured by EGDS), as well as hernia with Cameron erosion [18, 20, 21, 22]. Large hiatal hernias are responsible for IDA in 9.2% of patients, with Cameron's erosion present in one third of patients [23]. In our study, hiatus hernia was a diagnostic finding only if it was ≥ 4 cm with Cameron erosion, which was present in 2.4% of the patients.

A study by Majid et al. [24] found that the most common causes of IDA in the upper part of the GIT were erosive gastritis (8.4%), erosive esophagitis (6.3%), gastric (5.3%), and duodenal ulcer (5.3%). In the same study, the most common causes in the lower part of the GIT were colonic ulcers (4.3%), colonic mass (2.1%), and colonic polyps (2.1%) [24].

Rockey et al. [9] found that the causes of IDA in the upper part of the GIT were duodenal ulcer (11%), esophagitis (6%), gastritis (6%), gastric ulcer (5%), vascular ectasias (3%), anastomosis ulcer (3%), gastric cancer (1%), and other causes (2%) [9]. Furthermore, they found that the most common cause of IDA in the lower part of the GIT was colon cancer (11%), polyps (5%), vascular ectasias

### Table 4. Pathological and diagnostic finding of colonoscopy (n = 61)

| Finding                        | %   | n  |
|-------------------------------|-----|----|
| Colon neoplasm                | 19.6| 12 |
| Inflammatory bowel disease    | 14.7| 9  |
| Hemorrhoids*                  | 9.8 | 6  |
| Colonic polyps*               | 9.8 | 6  |
| Diverticulosis*               | 8.1 | 5  |
| Angiodysplasia                | 6.5 | 4  |
| Post radiation colitis        | 4.9 | 3  |
| Resected colon*               | 3.2 | 2  |
| Colonic ulcer                 | 1.6 | 1  |

Bold – pathological and diagnostic finding; *pathological but not diagnostic finding for iron deficiency anemia

### Table 5. Diagnostic finding of esophagogastroduodenoscopy and colonoscopy in relation to patient characteristics

| Variable                        | EGDS diagnostic finding | Colonscopy diagnostic finding |
|---------------------------------|-------------------------|-------------------------------|
|                                 | % | n | p | % | n | p |
| Age 50 years                    | 13.9 | 5 | 0.031 | 37.9 | 11 | 0.243 |
| Female sex                      | 52.8 | 19 | 0.957 | 48.3 | 14 | 0.622 |
| Malaise and/or fatigue          | 88.6 | 31 | 0.454 | 82.8 | 24 | 0.693 |
| Syncope                         | 3.8 | 1 | 0.644 | 0 | 0 | 0.279 |
| Weight loss                     | 46.4 | 13 | 0.853 | 58.6 | 17 | 0.046 |
| Loss of appetite                | 7.7 | 2 | 0.517 | 7.4 | 2 | 0.205 |
| Abdominal pain                  | 56.7 | 17 | 0.339 | 55.2 | 16 | 0.256 |
| Dyspepsia                       | 24 | 6 | 0.932 | 17.2 | 5 | 0.313 |
| Heartburn                       | 12.3 | 3 | 0.288 | 17.2 | 5 | 0.865 |
| Tympanites                      | 10 | 2 | 0.335 | 13 | 3 | 0.434 |
| Vomiting                        | 7.7 | 2 | 0.273 | 17.2 | 5 | 0.298 |
| Irregular bowel emptying        | 34.5 | 10 | 0.271 | 59.3 | 16 | 0.012 |
| Active overt gastrointestinal bleeding | 47.2 | 17 | 0.120 | 37.9 | 11 | 0.082 |
| Arterial hypertension           | 44.4 | 16 | 0.842 | 39.3 | 11 | 0.154 |
| Diabetes mellitus               | 6.2 | 2 | 0.062 | 17.2 | 5 | 0.415 |
| Arrhythmia                      | 14.3 | 5 | 0.902 | 14.3 | 4 | 0.260 |
| Cerebrovascular insulin         | 9.4 | 3 | 0.572 | 3.4 | 1 | 0.074 |
| Gastritis                       | 12.5 | 4 | 0.144 | 24.1 | 7 | 0.992 |
| Ulcer disease                   | 15.6 | 5 | 0.192 | 6.9 | 2 | 0.270 |
| GERD                            | 6.3 | 2 | 0.365 | 3.4 | 1 | 0.721 |
| Malignancies*                   | 6.3 | 2 | 0.522 | 13.8 | 4 | 0.043 |
| Overt gastrointestinal bleeding in past medical history | 69.6 | 16 | 0.404 | 71.4 | 10 | 0.652 |
| Iron preparations               | 27.8 | 10 | 0.961 | 20.7 | 6 | 0.022 |
| Acetylsalicylic acid            | 27.6 | 8 | 0.805 | 17.2 | 5 | 0.313 |
| Nonsteroidal anti-inflammatory drugs | 20 | 6 | 0.191 | 13.8 | 4 | 0.289 |
| Anti-platelet drugs             | 21.2 | 7 | 0.582 | 10.3 | 3 | 0.289 |
| Alcohol consumption             | 6.7 | 2 | 0.577 | 3.4 | 1 | 0.357 |
| Anemia in past medical history  | 80 | 20 | 0.198 | 47.8 | 11 | 0.001 |
| Malignancies in family history  | 15.4 | 4 | 0.208 | 26.9 | 7 | 0.827 |
| Pallor                          | 52.8 | 19 | 0.803 | 48.3 | 14 | 0.482 |
| Abdominal tenderness            | 33.3 | 12 | 0.945 | 34.5 | 10 | 0.877 |
| Hepatomegaly                    | 8.3 | 3 | 0.384 | 10.3 | 3 | 0.259 |
| Asceres                         | 2.8 | 1 | 0.688 | 0 | 0 | 0.178 |
| Pathological finding of digital rectal examination | 40 | 10 | 0.502 | 31.8 | 7 | 0.367 |
| FOBT positive                   | 36.8 | 7 | 0.866 | 66.7 | 12 | 0.012 |

Bold – p < 0.05; EGDS – esophagogastroduodenoscopy; GERD – gastroesophageal reflux disease; FOBT – fecal occult blood test; EGDS – esophagogastroduodenoscopy; *malignancies in past medical history

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(5%), colitis (2%), cecum ulcer (2%), and parasite infestation (1.05%). In contrast to these studies, we found that the most common lesion underlying IDA in the upper GIT was gastric and/or duodenal angiodysplasia. The explanation for these results is multifactorial. We collected data on patients who were examined at a tertiary care institution, to where patients are generally referred when diagnosis and/or treatment cannot be carried out at the primary or the secondary level. Our sample included patients with an average age of about 60 years, and angiodysplasias are more common in the older population [25]. The average age of subjects in the study by Rockey et al. [9] was 60 ± 14 years, which is very similar to our sample; however, that study was conducted in the 1990–1992 period.

One third of our patients had a non-diagnostic finding of endoscopy. Based on recent literature data, 10–41% of IDA patients have a negative finding of endoscopy [26, 27]. The cause of the negative finding is also multifactorial; namely, anemia can be caused by a lack of iron in the diet, other organ and systemic diseases, significant lesions overlooked during endoscopy, and/or lesions unavailable to endoscopy (especially lesions in the small intestine). Exploration of the small bowel is indicated in patients who are transfusion-dependent or have persistent symptoms [28].

Our research concluded that the diagnostic finding on EGDS was significantly more frequent in patients older than 50 years, which is in line with previously published results [8, 13, 19, 24]. These results can be explained by the fact that GIT disorders, which cause chronic bleeding, are more common in the older population.

More than one half of our patients had symptoms specific to the digestive system, supporting previously published results [8]. By analyzing the effects of individual symptoms on a positive endoscopic finding, we concluded that weight loss and irregular bowel emptying were more frequent in patients with a diagnostic finding on colonoscopy. This is a logical conclusion considering that the highest percentage of our patients with a positive colonoscopy finding had colonic carcinoma or inflammatory bowel disease, and that weight loss and irregular bowel emptying form the basis of the clinical presentation of these conditions. Literature on abdominal symptoms and diagnostic endoscopic findings are contradictory. Rockey et al. [9] concluded that abdominal symptoms are associated with a pathological finding, adding that, symptoms “specific to the side” were specific for a positive finding of endoscopy of that respective side, whereas the absence of such symptoms did not exclude pathological changes on that side. Supporting the predictive significance of abdominal symptoms in the diagnosis found on endoscopy are the results of Nahon et al. [8] and of Carter et al. [15]. In contrast, however, Friedman et al. [12] found no significant correlation between abdominal symptoms and endoscopic findings.

The use of alcohol as well as non-steroidal anti-inflammatory drugs were not associated with a higher incidence of EGDS and colonoscopy diagnostic findings amongst our patients, which is consistent with the results of other studies [9]. Furthermore, the use of other investigational drugs did not indicate a significant association. The exception was the use of iron preparations; namely, we found that patients who used iron supplementation, alongside those with anemia in their history, had a significantly lower occurrence of diagnostic findings on colonoscopy.

We concluded that a positive personal history of malignancy was associated with a higher incidence of a diagnostic finding of colonoscopy.

Our study had limitations. We did not have information about the patient's H. pylori status, and H. pylori infection can play an important role in IDA [29, 30]. The study included patients who were examined in a tertiary institution, so selection bias cannot be excluded.

CONCLUSION

Diagnostic findings on EGDS in patients with IDA was more common in older patients, while a diagnostic finding on colonoscopy was more frequent in those with presenting symptoms of weight loss, change in bowel habit, positive FOBT and malignancy in their personal history. Patients who had no history of anemia, and did not consume iron preparations previously, were more likely to show diagnostic findings on lower endoscopy.

NOTE

This manuscript was partially presented as an abstract “Endoscopy in patients with iron deficiency anemia,” ESGE Days 2018, April 19–21, 2018, Budapest (Endoscopy 2018; 50(04): S159). The manuscript is part of the postgraduate (subspecialist) thesis titled “Esophagogastroduodenoscopy and colonoscopy in patients with anemia due to iron deficiency,” which was finished in 2016.

Conflict of interest: None declared.

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Горња и доња гастроинтестинална ендоскопија код болесника са анемијом услед недостатка гвожђа

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САЖЕТАК
Увод/Циљ
Сазнања о унутрашњој употреби гастродуоденог (ЕГДС) и колоноскопије код болесника са анемијом у связи са настојањем и налазима и манипулацијама које биле прилагођене болеснику. Зацијелио се анализом чланака који су се бавили гастродуоденом и колоноскопијом у потичући на унутрашњу гастродуоденалну недостатак гвожђа.

Методе
Спрудена је ретроспективна студија у којој су били укључени болесници са анемијом. Уклоњена су азимутална и кулипаза у случају који се укупно уклоњено 85 болесника са анемијом. Смештено настала анемија била је карактеристична за 47,5% болесника. Унапред боље покушање у могућност узгоја гастродуоденалне анемије било је карактеристично за 47,5% болесника са анемијом.

Закључак
Дијагностички налаз ЕГДС је карактеристичан код болесника са анемијом, али је уместо гастродуоденалне анемије карактеристичан код 47,5% болесника. Дијагностички налаз ЕГДС је био прилучан код 43,9% болесника, колоноскопија код 47,5%, док је карактеристичан код 47,5% болесника.

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