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Original Article

Internal Medicine Section

Upper and Lower Gastrointestinal Endoscopic Lesions in Patients with Unexplained Iron Deficiency Anaemia- A Cross-sectional Study

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ABSTRACT

Introduction: Anaemia, due to iron deficiency, is very common in India. In many cases, the underlying cause of iron deficiency remains unknown even after detailed laboratory investigations. It is often due to malabsorption of iron from the gut and occult blood loss from the Gastrointestinal (GI) tract. Bidirectional GI endoscopy can help in finding these causes.

Aim: To study the upper and lower GI endoscopic lesions in patients with unexplained Iron Deficiency Anaemia (IDA).

Materials and Methods: This was a cross-sectional observational study, conducted on 75 patients with unexplained IDA in Dr. DY Patil Medical College and Hospital, Pune, Maharashtra, India, between June 2019 to June 2020. Patients above the age of 18 years and with Haemoglobin (Hb) of less than 13 g/dL (males) and less than 12 g/dL (females) underwent upper GI endoscopy and colonoscopy with biopsies, after ethics committee approval and informed consent. Complete haemogram with blood indices, iron studies and faecal Occult Blood Test (OBT) were conducted for all the patients. The patients were divided into Group A, those with upper/lower GI endoscopy lesions thought to be responsible for IDA and Group B, those without GI endoscopic lesions. Statistical analysis was performed using IBM, Statistical Package for the Social Sciences (SPSS), version 21.0 and statistical tests (Chi-square test, Student's t-test and multivariate logistic regression analysis, with 95% Confidence Interval (CI) and p-value <0.05 was taken as significant) were used when required.

Results: There were 44 females and 31 males in the study, with the age range of 20-81 years. The mean age of patients in Group A (n=44) was 58.57±11.68 years and Group B (n=31) was 49.68±14.45 years. On multivariate analysis, advance age, history of weight loss and faecal occult blood were statistically significantly associated with the presence of GI endoscopic lesions responsible for IDA (p-value<0.05). Maximum lesions responsible for IDA were found in stomach (48%), erosive and inflammatory lesions causing IDA were more common in upper GI tract. Peptic ulcers were found in 12% cases. The GI malignancies were found in 14.66% subjects. Colorectal cancers (8%) were more common than upper GI cancers (6.66%).

Conclusion: In patients with IDA, erosive oesophagitis and haemorrhagic gastritis were commonly found followed by peptic ulcers and malignant GI lesions on bidirectional endoscopy. GI endoscopy is a very important tool to diagnose the cause of IDA. All patients with advanced age, history of weight loss and a positive faecal OBT should undergo bidirectional GI endoscopy routinely.

Keywords: Colorectal neoplasms, Endoscopy, Gastritis, Occult blood test, Peptic ulcer

INTRODUCTION

Iron is an essential element for various functions of the body like cellular growth, differentiation, oxygen binding, enzymatic reactions, immune functions and cognitive functions. So, deficiency of iron either due to physiological or pathological reasons can affect mental and physical growth resulting in decreased quality of life.

More than half of the total anaemia cases (two billion) in the world are due to iron deficiency as per the World Health Organisation (WHO) [1]. Anaemia occurs in late stages of iron deficiency and thus, on estimation the prevalence of iron deficient state is 2.5 times more than IDA [2,3]. The prevalence of IDA in developing countries is 42% in women of child-bearing age (15-59 years), 45% in geriatric population (above 60 years) and 30% in adult males [1]. Iron deficiency causes substantial physical productivity losses in population [2].

Occult Gastrointestinal (GI) bleeding is a common cause of IDA. Recent evidence suggests that most of patients with IDA have a significant GI tract pathological lesion [4]. The evaluation of patients with unexplained IDA and without any obvious bleeding should include the GI tract. American gastroenterological association recommends bidirectional endoscopy, i.e., both oesophagogastroduodenoscopy and colonoscopy [5].

In population above 50 years of age, screening of the upper and the lower GI tract is advised, regardless the presence of anaemia [6]. A study on 100 patients from southern India found that GI lesions were present in nearly 3/4th of the patients (73.3%) [7]. A recent study by Kumar A et al., in a north eastern Indian Hospital found that a total of 51.78% patients had lesions on upper GI endoscopy responsible for IDA and 36.67% patients had lesions on colonoscopy causing IDA [8]. Both the studies concluded that bidirectional GI endoscopy is an important investigation to be done in all the patient with IDA especially elderly.

Patients with IDA have a high prevalence of malignant lesions of the GI tract and therefore, it has been suggested that bidirectional endoscopy in unexplained IDA patients will lead to early diagnosis and better outcomes in GI tract cancers [9]. Also, in developing countries where medical resources are limited, often the GI endoscopy provides the diagnosis and cause of IDA thus, avoiding invasive investigations like bone marrow biopsies. Nowadays, with advanced options for local oral anaesthesia and light sedation during the bidirectional GI endoscopies, patients readily undergo the procedures which have become relatively painless and less invasive.

The current study was done with the aim to determine the GI causes of iron deficiency by doing both upper and lower GI endoscopies with biopsies.

MATERIALS AND METHODS

This cross-sectional observational study was conducted in a tertiary care Dr. DY Patil Medical College and Hospital, Pune, Maharashtra, India, June 2019 to June 2020 after taking approval from Institutional Scientific and Ethics Committee (Letter Number: IESC/PGS/2018/138).

Inclusion criteria: Total 365 patients, aged ≥18 years admitted in the medical wards were found to have IDA. The criteria used for diagnosis of iron deficiency were males with Hb <13 g/dL and females with Hb <12 g/dL and iron studies showing serum ferritin concentration ≤20 ng/mL for men and ≤10 ng/mL for women. After initial investigations, obvious causes for IDA, (like blood loss, malnutrition, anaemia of chronic diseases and pregnancy) were not found in 114 patients. Patients with active and identifiable source of blood loss (active GI loss, epistaxis, menorrhagia), chronic kidney and liver disease, pregnancy, active malignancy anywhere in the body, steroids and Non Specific Anti Inflammatory Drugs (NSAIDs) therapy within eight weeks prior to commencement of the study, coagulation and bleeding disorders were excluded from the study.

Exclusion criteria: Out of 114 patients, 39 patients were excluded from study because seven patients had chronic kidney disease, six patients had liver disease, eight patients had history of NSAIDs intake, five patients had active GI blood loss, four patients were immunocompromised, four patients were pregnant, four patients had active malignancy and one patient had coagulation disorder. Thus, a total of 75 patients were studied after taking a written informed consent from them.

Study Procedure

A detailed clinical history and general physical examination was done. All the study subjects (n=75) underwent the following laboratory investigations i.e, complete haemogram with blood indices (Hb, total and differential leukocyte counts, Erythrocyte Sedimentation Rate, Platelet count, Red Blood cell count (RBC), Red Cell Distribution Width (RDW), Packed Cell Volume (PCV), Reticulocyte and Corrected Reticulocyte count, Mean Corpuscular Volume (MCV), Mean Corpuscular Haemoglobin (MCH), Mean Corpuscular Haemoglobin Concentration (MCHC), Iron studies (Serum Ferritin, Serum Iron, TIBC, percentage saturation of transferrin), stool examination for occult blood. All the patients underwent GI endoscopy after due consent, under local anaesthesia and minimal sedation, if required. Light source of Fujinon Epx-2200 and video gastroscope fujinon Model number- EG-250WR5 for Upper GI Endoscopy and Fujinon EC-530-LS 11.5-mm×160-cm videoscope with 3.8-mm operating channel for Lower GI Endoscopy were used. Gross findings were noted. Biopsies were taken from oesophagus (lower 1/3rd), stomach (fundus, body and antrum), duodenum 2nd part (D2) and from the affected areas of colon during colonoscopy as and when required. The biopsy samples were sent for histopathological confirmation of diagnosis.

The patients were divided into two groups- Group A had those in which upper/lower GI endoscopy showed lesions responsible for IDA, group B had those without GI endoscopic lesions..

STATISTICAL ANALYSIS

Data were expressed as counts, percentage and/or mean±standard deviation. Statistical analysis was performed using IBM, SPSS, version 21.0. All tests were two tailed with 95% CI (confidence interval). Results were considered statistically significant if p-value was less than 0.05. Chi-square test, student's t-test and multivariate logistic regression analysis were the tests used.

RESULTS

Maximum (36.7%) study subjects were in age group of 50-59 years. Mean age of study subjects were 54.86±13.53 years and the age range of study subjects was 20-81 years. A total of 44 subjects were females (58.7%) and 31 were males (41.3%). Thirty out of thirty four females (88.2%) were postmenopausal and 11.8% were in the child-bearing age. A total of 33 patients had tobacco addiction alone. Both tobacco and alcohol addictions was present in 15 patients. History of weight loss was present in 58 cases (77.33%). Easy fatiguability and generalised weakness was found in 52 patients. Stool OBT was found to be positive in 44 out of 75 cases (58.7%).

Among the two study groups, 44 (58.7%) cases belonged to Group A (had GI lesions responsible for IDA) and 31 (41.3%) cases belonged to Group B (no GI lesion responsible for IDA was detected on bidirectional endoscopy). [Table/Fig-1] shows various demographic and laboratory parameters in the two sub-groups.

Parameters	GI lesions responsible for IDA found (Group A, n=44) (Mean±SD)	GI lesions not found (Group B, n=31 (Mean±SD)	p-value
Age (years)	58.57±11.68	49.68±14.45	0.011*
History of weight loss (n)	40	18	0.001*
Haemoglobin (g/dL)	7.5±1.8	7.8±1.4	0.573
Total leukocyte count (/µL)	6562.9±1671.6	7304.0±1657.2	0.095**
Red blood cell count (10^6/µL)	3.5±0.7	3.6±0.6	0.579**
Packed cell volume (%)	23.1±5.8	24.6±5.1	0.309**
Mean corpuscular volume (fL)	65.5±7.3	68.8±4.7	0.051**
Mean corpuscular haemoglobin (pgms)	21.3±3.3	21.8±2.3	0.473**
Mean corpuscular haemoglobin concentration (g/dL)	32.6±4.2	32.0±3.9	0.548**
Red cell distribution width (%)	19.8±2.8	19.1±2.7	0.33**
Corrected retic count (%)	0.9±0.5	1.0±0.4	0.508**
Faecal occult blood positive (n)	40/14	4/17	0.001*
Serum Iron (g/dL)	25.21±0.5	27.0±7.8	0.543**
Transferrin saturation (%)	0.3±1.5	0.1±0.01	0.402**
Serum ferritin (ng/dL)	9.2±5.0	10.4±4.9	0.331**
Total iron binding capacity (g/dL)	410.2±20.5	412.2±12.3	0.668**

[Table/Fig-1]: Demographic and laboratory parameters in the study subjects.
p-value <0.05 considered statistically significant; *is Chi-square test,**Student's t-test

There was no statistically significant difference in mean value of biochemical parameters among two groups using t-test (p-value <0.05). Among demographic variables patient's age, history of weight loss and faecal occult blood had statistically significant association with the presence of endoscopic GI lesions responsible for IDA based on using chi-square test (p-value <0.05).

Serum iron studies were compared between the two sub-groups using student's t-test and there was no statistically significant difference in the mean values of serum iron, transferrin saturation, serum ferritin, and total iron binding capacity among both the groups (p-value>0.05). [Table/Fig-2] shows gross and Histopathological Examination (HPE) findings as seen during upper and lower GI endoscopies in the study subjects.

Erosive and haemorrhagic lesions of the upper GI tract and colitis in the lower GI tract were the most common gross findings during endoscopy [Table/Fig-2].

Maximum lesions responsible for IDA were found in stomach (n=37, 49.3%), followed by oesophagus (n=33, 44%), and duodenum (n=25, 33.33%). Colonic lesions responsible for IDA were found in 10.6% patients. *Helicobacter Pylori* was detected on histopathology of antral biopsy specimen in 24 patients (32%) cases.

Site in GI	Gross and HPE findings	Number of patients (n=75)	Percentage (%)
Oesophagus	Normal	42	56
	Erosive oesophagitis	19	25.4
	Hiatus hernia with erosions	5	6.6
	Oesophageal varices	5	6.6
	Oesophageal mass lesion	2	2.7
	Oesophageal candidiasis	2	2.7
Stomach	Normal	38	50.6
	Haemorrhagic antral/ pan/erosive gastritis	21	28
	Gastric ulcer	4	5.3
	Portal hypertensive gastropathy	4	5.3
	Gastric varix	3	4
	Gastric mass lesion	3	4
	Gastric polyp	1	1.4
	Gastric antral vascular ectasia	1	1.4
Duodenum (D1/D2)	Normal	50	66.66
	Erosive duodenitis	20	26.67
	Duodenal ulcer	5	6.67
Lower GI tract	Normal study	42	56
	Colitis	23	30.66
	Colonic mass lesion	2	2.67
	Hyperplastic/tuberous polyp	2	2.67
	Rectal mass lesion	2	2.67
	Internal haemorrhoids	2	2.67
	Ileo-caecal tuberculosis	1	1.33
	Intestinal diverticula	1	1.33

[Table/Fig-2]: Upper GI and lower GI gross findings on endoscopy (Gross and HPE).
HPE: Histopathological examination; GI: Gastrointestinal

The HPE confirmed GI tract malignant masses were found in 14.66% subjects. HPE confirmed the lesions as oesophageal adenocarcinoma (1.3%), oesophageal squamous cell carcinoma (1.3%), and adenocarcinoma stomach (4%). Colon carcinoma was found in 8% cases (adenocarcinoma colon (5.33%) and adenocarcinoma rectum (2.67%). Colorectal malignant lesions (8%) were more common than upper GI malignant lesions (6.66%) [Table/Fig-3].

HPE confirmed malignancy	n	Percentage (%)
Oesophagus and stomach	5	6.66
Colon and rectum	6	8

[Table/Fig-3]: HPE confirmed malignant lesions found in the study subjects.
HPE: Histopathological examination

On multivariate logistic regression analysis after adjusting for confounding factors, positive faecal occult blood (OR 25.48, 95% CI 4.52-143.71) and weight loss (OR 7.73, 95% CI 1.12-53.20) were independent predictors of lesions responsible IDA on bidirectional endoscopy.

DISCUSSION

The IDA is the most common cause of anaemia. The treatment of unexplained IDA remains a challenge. Bidirectional GI endoscopy may help to elucidate the cause of unexplained IDA as it could be due to occult GI blood loss or other GI lesions. There are relatively few research studies on the bidirectional endoscopic findings in unexplained IDA on subjects of Indian ethnicity. Current study aimed to bridge this gap in research on Indian subjects in whom IDA is prevalent.

This study had more female subjects than males. Weight loss (77.33%) and easy fatiguability (69.33%) were the common symptoms at the presentation. Haemorrhagic and erosive gastritis (28%) was the common finding on upper GI endoscopy UGIE. Addiction to tobacco and alcohol which was present in nearly two thirds (64%) of the study subjects may have contributed to the inflammation of the gastric walls. Colonic inflammation was the common finding on colonoscopy (30.66%).

Out of 75 patients, in 44 (58.66%) patients the bidirectional GI endoscopy revealed the cause of IDA (Group A). Isolated upper GI lesions were found in 80%, isolated lower GI lesions in 13.3% and both upper and lower GI lesions in 6.6% cases. In a study by Niv E et al., bidirectional endoscopies and CT of abdomen detected the cause of IDA in 71% cases. Twenty-nine percent patients had upper GI lesions alone, 33% had lesions in lower GI tract alone and 6% had lesions both in upper as well as lower GI tract which explained their anaemia [10].

Patients belonging to Group A (n=44) had lower mean Hb, MCV and S. Ferritin levels. In a similar study by Majid S et al., bidirectional endoscopy revealed the cause of unexplained IDA in 51 out of 95 patients and they too had lower mean Hb, MCV and S. Ferritin levels [11]. The findings were similar in a study by Nahon S et al., [12]. It can thus be inferred that GI lesions increase the severity of iron deficiency state in the body.

Positive faecal OBT in patients with iron deficiency should prompt the treating physician to thoroughly investigate both the upper and lower GI tract as evidenced by the high rate of positive faecal OBT in cases with GI lesions (Group A 90.9% had positive Faecal OBT) in the current study. Study by Majid S et al., corroborate this finding [11]. Oesophagitis (25.4%) was the most common finding followed by Varices (6.7%), hiatus hernia (6.7%) and oesophageal mass lesions (2.7%) in this study. In other similar studies oesophagitis was found in 14% and 6.3% cases, respectively [10,11]. In a study done in Jaipur, India, 26% cases had oesophagitis and 4.67% had oesophageal varices [13].

The most common UGIE finding was haemorrhagic erosive gastritis (28%) which was similar to the findings of other European and an Indian study [10,11,13]. Common causes of erosive gastritis are NSAIDs abuse, alcoholism, stress induced erosions like in burns and portal hypertension [14]. Erosions in the stomach wall may bleed continually and contribute to the severity of IDA.

Inflammatory, ulcerative and malignant GI lesions were the most common UGIE findings in our study. These findings were similar to the results of many studies where GI endoscopic evaluation was done for IDA [10,15-18]. None of the patients had inflammatory bowel disease in this study on colonoscopy. Current study found colonic lesions responsible for IDA in nearly 8% cases. Zukerman G and Benitez conducted a study on 100 patients with occult GI bleed. They found that 6% cases had colorectal malignancy on colonoscopy [18]. In another study by Rockey DC et al., done on 248 patients who underwent bidirectional endoscopy for positive faecal OBT, 13 patients (5.24%) had colon carcinoma [9]. In the present study, GI lesions responsible for IDA were most found in the stomach on endoscopy (45%) followed by the oesophagus (31.66%). Both upper and lower GI lesions were present together in 5 cases (6.66%). In a study on total 95 patients by Majid S et al., GI lesions responsible for IDA were found in total 52.6% cases. Lesions were most found in stomach (22.5%) followed by oesophagus (10.5%) and colon (10.5%). Both upper and lower GI lesions were present in 1.1% cases. Endoscopic lesions were predominantly in upper GI tract [11]. In another study by Niv E et al., lesions responsible for IDA were mostly found in lower GI tract (33%) [10].

In the present study, four cases had malignant lesions (two in the oesophagus and three in the stomach) on UGIE. Total 14.66% patients with unexplained IDA had malignant GI lesions found during bidirectional endoscopy. Adenocarcinomas were the most common histological type in this study. The prevalence of malignant GI lesions in unexplained IDA differ in various studies. In a study by Rockey DC et al., the prevalence of gastric carcinoma was 1.6% and colonic carcinoma was 5.2% [9]. In a study of GI lesions in IDA by Cook IJ et al., malignancy was present in 12% cases which were responsible for the anaemia [19].

Different studies have estimated that colon carcinoma accounts for 11-14% and stomach carcinoma accounts for around 1-5% of IDA in some of the western countries [9,19-21]. The prevalence of gastric and colorectal adenocarcinomas was 2.44% in immigrant Asian population in a study done in the US. However, there was no association between the presence of endoscopic GI lesions and anaemia in these patients [22]. In another Chinese study, 61 patients with IDA underwent bidirectional GI endoscopy and eight (13.11%) patients had gastric and colon cancers among them [23]. Accurate Indian data on the prevalence GI cancers in unexplained IDA patients is lacking. However, an Indian study done by Pandey A et al., where 311 patients with cancers were evaluated for the presence of IDA, it was found that total 22.2% cancer patients had GI malignancies and more than 70% of them had iron deficiency [24]. As the GI malignancies are often slow growing and asymptomatic with the only symptom being anaemia, complete investigation of the GI tract by bidirectional endoscopy in patients presenting with anaemia is warranted [25].

After malignancy, peptic ulcer disease was the common cause of anaemia in the present study. *Helicobacter pylori* was detected on histopathology in 31.7% cases. It reflected higher prevalence of *Helicobacter pylori* infection in the population which matches with the findings of the study by Ahmad MM et al., [26]. *Helicobacter pylori* infection has recently been found to be a potential cause for IDA, refractory to oral iron but amenable to treatment after *Helicobacter pylori* eradication in several recent studies [27-29]. In a study by Serefhanoglu S et al., 19.8% had *Helicobacter pylori* gastritis [15]. Hershko C et al., showed that among 150 patients, 19% study subjects had *Helicobacter pylori* infection [30].

Ileo-caecal tuberculosis was diagnosed in one patient in the current study. Anaemia in GI tuberculosis is due to occult GI bleed from the TB ulcers, malabsorption of dietary iron and due to anaemia of chronic disease [9]. Tuberculosis being common in the country and the signs and symptoms of GI TB being non specific, a high index of suspicion should be maintained for early diagnosis and treatment.

On univariate analysis, in the present study, age, history of weight loss and a positive faecal OBT were the significant factors associated with GI lesions responsible for IDA. In the current study, presence of weight loss and positive faecal occult blood were the independent predictors for IDA lesions in GI endoscopy (On multivariate logistic regression analysis). Age of the patient was not a predictor of IDA.

In a study by Majid S et al., on multivariate logistic regression analysis after adjusting confounding factors and with a confidence interval of 95%, age (OR 1.04, 1.01-1.08), MCV ≤ 60 fl (OR 14.8, 3.6-60.7) and positive faecal OBT (OR 7.8, 1.46-41.8) were independent predictors of the cause of IDA on bidirectional GI endoscopy [11].

Limitation(s)

Small sample size, selection bias, observer bias since gross endoscopic findings are often subjective were the few limitations of the study. We did not evaluate the small bowel and hence may have missed its pathology.

CONCLUSION(S)

The IDA was commonly seen in post-menopausal females and elderly males. GI lesions responsible for IDA were most frequently found in the stomach followed by oesophagus, duodenum and the colon. Erosive and haemorrhagic inflammatory lesions of the GI tract, peptic ulcers and malignant lesions were commonly associated with unexplained IDA. History of weight loss and positive faecal OBT independently predicted the presence of GI lesions responsible for IDA.. Therefore, patients of IDA with advanced age, history of weight loss and positive faecal OBT should undergo GI evaluation with bidirectional endoscopy. Thus, to conclude, bidirectional GI endoscopy is an important tool in the evaluation of unexplained IDA. It can aid in early detection of life threatening diseases like GI malignancies.

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