

## ORIGINAL ARTICLES

## EVALUATION OF PATIENTS WITH UNEXPLAINED ANAEMIA AND GASTROINTESTINAL SYMPTOMS

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**Background and Aims:** A number of patients presenting with anaemia are referred to gastroenterologist for evaluation. Literal sense of unexplained anaemia is anemia of unknown origin, which is widely used by the clinicians. Aims of this study were to determine the underlying cause of unexplained anemia and to identify clinical features that may point to primary gastrointestinal diseases.

**Methods:** All the patients presenting with anaemia admitted in the department of Gastroenterology from January 1990 to July 2001 were enrolled for this study.

**Results:** Sixty two patients were included in this study, twenty two were Collected retrospectively and forty were collected prospectively. The mean Age was 43 years (SD  $\pm$  14.8, range 15–72 years). Twenty eight of the Patients were male, remaining thirty four were female. The mean duration of the illness was 26.3 months (SD  $\pm$  41.8, range 1–240 months) and the Mean haemoglobin was 6.4 gm/dl (SD  $\pm$  1.2, range 3.5–9 gm/dl). Among 62 patients, gastrointestinal causes for anaemia were found in 32 (51.62%) patients. Seventeen (27.41%) patients had a disease outside gastrointestinal tract; in thirteen (20.96%) patients no cause for anaemia could be established. Gastrointestinal malignancy was the most common finding, Gastrointestinal tuberculosis was the next. Symptoms had a sensitivity and Specificity of upper gastrointestinal disease of 64% and 36% respectively, and 30% and 82% for colonic disease.

**Conclusions:** Gastrointestinal malignancy frequently presents with unexplained anaemia. Symptoms are poor predictors for site specific lesion. The standard evaluation of a patient with unexplained anaemia includes a complete evaluation of the gastrointestinal tract. However, even after extensive investigations many patients may remain without a diagnosis.

**Key words:** unexplained anaemia, gastrointestinal symptoms, Bangladesh

**Introduction**

Anaemia is a common clinical condition in Bangladesh. In some of these patients the cause of anaemia cannot be established at the primary care level. Facilities for investigation are limited at primary and even secondary care levels in Bangladesh, hence a larger proportion of these patients attend referral centres. Some of these patients have associated gastrointestinal symptoms which results in referral to Gastroenterology units.

A number of gastrointestinal diseases may cause anaemia. These include diseases in which there is gastrointestinal blood loss (such as peptic ulcer

disease, colorectal carcinoma etc.) and malabsorptive disorders (such as tropical sprue, bacterial colonization of the gut etc.). These diseases may present with symptoms referable to the gastrointestinal tract in addition to anaemia. In Western countries, iron deficiency anaemia is commonly caused by chronic blood loss from the gastrointestinal tract<sup>1</sup>. Disease of other systems presenting with anaemia may also have gastrointestinal manifestations. Patients presenting with anaemia and gastrointestinal symptoms may have primary gastrointestinal diseases or diseases of other systems.. We studied a group of patients presenting with anaemia and gastrointestinal

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symptoms to find out the underlying cause and to identify features which may point to primary gastrointestinal diseases.

**Patients and Methods**

All patients presenting with anaemia who were admitted in the department of Gastrointestinal, Liver and Pancreatic Diseases of the then IPGMR (Institute of Postgraduate Medicine and Research), at present Bangabandhu Sheikh Mujib Medical University, Dhaka from January 1990 to July 2001 were enrolled for this study. Twenty two patients were collected retrospectively and forty patients were collected prospectively. They had been investigated previously to varying degrees by general practitioners but investigations failed to find a cause.

Patients were excluded from the study if they had a known cause of blood loss, or had been taking nonsteroidal anti-inflammatory drugs regularly, or had an established reason for anaemia. Pregnant ladies and lactating mothers were not included in this study.

Gastrointestinal symptoms were grouped into upper and lower gastrointestinal symptoms. Upper gastrointestinal symptoms which consisted of anorexia, nausea, vomiting, upper abdominal pain that was related to food or relieved by antacid or H<sub>2</sub> blocker. Lower gastrointestinal symptoms comprised of changed bowel habit, diarrhoea, constipation, lower abdominal pain that was colicky or associated with altered bowel habit or relieved by the passage of stool or flatus. The finding of an epigastric mass or hepatosplenomegaly was taken to suggest upper gastrointestinal disease while a mass in the right iliac fossa was taken to point to lower gastrointestinal disease. As gastrointestinal symptoms or signs may be nonspecific two or more features related to either the upper or lower tract were considered necessary to suggest the site of possible disease.

Anemia was assessed by estimating haemoglobin concentration in the blood and peripheral blood film

study. Serum ferritin concentration, serum iron concentration, total iron binding capacity, bone marrow aspiration, haemoglobin electrophoresis, reticulocyte count, RBC life span study, Schilling test, osmotic fragility test, Coomb’s test, liver function tests, kidney function tests, thyroid function tests, tuberculin test, X-ray chest were performed according to need.

The gastrointestinal investigations comprised of endoscopy of upper gastrointestinal tract, distal duodenal biopsy, barium follow through X-ray examination of the small gut, double contrast X-ray examination of the colon, sigmoidoscopy, colonoscopy, ultrasound examination of the abdomen, computed tomography (CT) of the abdomen, faecal occult blood test were performed when considered appropriate. Diagnostic laparoscopy or laparotomy was done when clinically indicated. Ethical clearance was obtained from institutional ethical review board. Informed consent was filled in respective cases.

**Results**

Sixty two patients were included in this study, twenty two patients were collected retrospectively and forty patients were collected prospectively. The mean age of the study group was 43 years (SD ±14.8, range 15-72 years). Twenty eight of the patients were male, remaining thirty four were female. The mean duration of the illness was 26.3 months (SD ±41.8, range 1-240 months) and the mean haemoglobin was 6.4 gm/dl (SD ±1.2, range 3.5-9 gm/dl).

Among 62 patients, gastrointestinal causes for anemia were found in 32 patients. Seventeen patients had a disease outside gastrointestinal tract, in thirteen patients no cause for anemia could be established.

Table I shows the relation between the age of the patients and the identified cause of anemia. Over half of the patients in whom no cause for anemia was found or in whom a systemic disease or a haematological cause was found were less than 45 years old. All the malignancies were in patients over 46 years old (range 46 - 75 years).

**Table-I**  
*Age distribution among different aetiologies of unexplained anemia with gastrointestinal symptoms.*

(Years)	n=13	Gastrointestinal cause		Diseases outside gastrointestinal tract	
		Malignancy n=11	Gastrointestinal diseases other than malignancy n=21	Malignancy n=04	Systemic diseases n=13
15-25	1	0	4	0	4
26-35	5	0	7	0	1
36-45	4	0	9	0	4
46-55	3	11	1	2	3
56-65	0	0	0	2	0
66-75	0	0	0	0	1

Table II shows gastrointestinal diseases other than malignancy associated with anemia in twenty one patients. Among them, nine patients presenting with anemia had tuberculosis. Of them eight had tuberculosis involving gastrointestinal tract, one had disseminated tuberculosis. Five of the nine patients with gastrointestinal tuberculosis had involvement of the terminal ileum and caecum and two had only colonic tuberculosis. Two of them had radiologic evidence and remaining three had no radiological evidence. Colonoscopy with biopsy allowed a definitive diagnosis of gastrointestinal tuberculosis in four patients, in one patient biopsy was not conclusive but presumptive diagnosis of gastrointestinal tuberculosis was made on the colonoscopic appearance of caecal ulceration and response to antituberculous therapy. One patient had peritoneal tuberculosis which was suspected on abdominal CT based finding of ascites and the diagnosis was made from the histology of the tissue obtained at laparoscopic biopsy. Diagnosis of disseminated tuberculosis was made in one patient who had evidence of both pulmonary tuberculosis and abdominal tuberculosis and responded to antituberculous therapy.

**Table-II**  
*Gastrointestinal diseases other than malignancy associated with unexplained anaemia and gastrointestinal symptoms (n=21)*

Tuberculosis	9
Post-gastric surgery malabsorption	4
Megaloblastic anaemia due to vit B <sub>12</sub> malabsorption	2
Leiomyoma of duodenum	1
Angiodysplasia of ileum	1
Gastric ulcer with haemorrhoid	1
Chronic liver disease with grade III esophageal varices	1
Colonic polyp	1
Inflammatory bowel disease	1
<b>Total</b>	<b>21</b>

There were four postgastroectomy anemic patients in whom gastric surgery for peptic ulcers had been performed a mean of 10.25 (SD ±5.5, range 10-19) years earlier. Two patients were diagnosed as a case of megaloblastic anemia due to vit B<sub>12</sub> Malabsorption. Dual pathology, gastric ulcer with haemorrhoid was found in one patient. One patient had chronic liver disease with marked esophageal varices. Six patients who had no positive yield from

routine investigations underwent colonoscopic examination. Despite the absence of colonic symptoms lesions were found in two cases by colonic assessment (adenomatous polyp and inflammatory bowel disease).

Seventeen patients had a disease outside gastrointestinal tract accounting for anemia (Table III). Haematological causes were the most common (congenital spherocytosis, haemoglobin E disease, acquired autoimmune hemolytic anemia due to hepatitis E virus and myelofibrosis). Three patients had malignancy outside gastrointestinal tract, those were renal cell carcinoma, multiple myeloma, acute myeloid leukemia and one had malignancy of unknown primary site which was diagnosed by laparoscopy and biopsy of peritoneal seedling.

**Table-III**

*Diseases outside gastrointestinal tract associated with unexplained anaemia and gastrointestinal symptoms (n=17)*

Haematological causes	6
Chronic renal failure	3
Hypothyroidism	2
Gynaecological cause (Cervical polyp-1 Fibroid uterus-1)	2
Malignancy of unknown primary site	1
Malignancy outside gastrointestinal tract	3
<b>Total</b>	<b>17</b>

Gastrointestinal symptoms were correlated with endoscopic findings to determine whether symptoms correctly indicated the need for upper gastrointestinal endoscopy or colonic assessment. Sixteen of thirty seven patients with upper gastrointestinal symptoms had lesions in the upper gastrointestinal tract at endoscopy, while nine of twenty one patients without any upper gastrointestinal symptoms had lesions in the upper gastrointestinal tract. In patients with anaemia, the positive predictive value of upper gastrointestinal symptoms for upper gastrointestinal lesions was 43%, negative predictive value was 57%. Three of five patients with lower gastrointestinal symptoms had lesions in the lower gastrointestinal tract, while seven of sixteen patients without any colonic symptoms had lesions at colonoscopic assessment. Positive predictive value for lower gastrointestinal symptoms for colonic lesions was 60% and negative predictive value was 56% in assessment of patients with anemia.

## Discussion

This study was conducted on 62 patients presenting with anemia of unexplained cause together with gastrointestinal symptoms. We retrospectively reviewed the records of twenty two patients and prospectively studied forty patients with anemia.

Thirty two (51.6%) of sixty two patients had a gastrointestinal disease contributing to anemia. Gastrointestinal malignancy was the most common finding. Carcinoma of stomach and colorectal cancer accounted for 8% and 4.8% respectively of identified lesions in this series. Different series have estimated that carcinoma of stomach accounts for 1-5%<sup>2,3</sup> and carcinoma of colon accounts for 11-14%<sup>2,3</sup> of iron deficiency anemia in Western countries. Although no data of prevalence of gastrointestinal malignancy in Bangladesh is available at present, this study reflects the relatively higher prevalence of carcinoma of stomach than colorectal cancer presumably because of higher prevalence of *Helicobacter pylori* infection in our population<sup>4</sup>. Anaemia was the only presenting manifestation in patients of duodenal adenocarcinoma, periampullary carcinoma, and ileal adenocarcinoma. Two case reports<sup>5</sup> and one study<sup>6</sup> has demonstrated the extreme latency of these tumours and the necessity for detailed gastrointestinal investigations in patients presenting with isolated iron deficiency anaemia including endoscopic examination of upper gastrointestinal tract, endoscopic retrograde cholangiopancreatography and colonoscopy.

Next to malignancy, gastrointestinal tuberculosis was the most frequent cause of anaemia. Anaemia in gastrointestinal tuberculosis may result from occult gastrointestinal bleeding from ulceration<sup>7</sup> or malabsorption of dietary iron or as a part of anaemia of chronic disease. Tuberculosis is common in our country. Sign and symptoms of gastrointestinal tuberculosis are nonspecific, a high index of suspicion must be maintained to ensure a timely diagnosis.

Seventeen patients (27.4%) had a disease outside gastrointestinal tract cause for anaemia. One previous study reported 2% patients had a systemic disease without co-existing gastrointestinal disease during evaluation of patients with iron deficiency anaemia<sup>2</sup>. This finding suggest that some patients presenting with anaemia and gastrointestinal symptoms may have disease outside the gastrointestinal tract. Systemic diseases such as chronic renal failure, hypothyroidism, haematological disorders may be considered during evaluation of patients with anaemia and gastrointestinal symptoms.

There were 13(20%) patients in whom no cause for the anaemia had been found. Some earlier studies have shown similar finding in patients with iron deficiency anaemia<sup>8,9,10</sup>. Follow-up data was not available in these patients. Most of these patients were asymptomatic. Conditions such as unreported menstrual losses or insufficient dietary intake of iron in the context of our poor socioeconomic status may have been responsible for occult iron deficiency. Alternatively, ulcerations or benign lesions might have caused blood loss in the past but then healed and thus were not detected. Moreover, abnormalities such as polyps or vascular ectasias might have been missed during the endoscopic examination or their anaemia was associated with undiagnosed chronic disease such as inflammatory bowel disease, rheumatoid arthritis etc. Up to 5% of patients with anaemia result from recurrent GI bleeding remains undiagnosed using gastroscopy and colonoscopy, with the presumed source of bleeding being the small bowel.<sup>11</sup> Until recently, various methods, including push enteroscopy, two-way enteroscopy, intra-operative enteroscopy, and capsule endoscopy have been employed to detect and manage small bowel lesions.<sup>12</sup> Several studies showed that capsule endoscopy is highly effective in detecting small-bowel lesions, with an overall diagnostic yield superior to that of push enteroscopy or radiologic imaging.<sup>13-16</sup> Capsule endoscopy is being recommended as the primary initial investigation in occult gastrointestinal bleeding by two international guidelines,<sup>17-19</sup> with DBE at present reserved for therapeutic action. Neither capsule endoscopy nor double balloon enteroscopy, mesenteric angiography are available in Bangladesh till todate. Therefore, small bowel pathology did not excluded in a number of patients. The extent to which the rest of the patients should be investigated further depends on their general health and age, symptoms related to anaemia and the need for continuing iron treatment or blood transfusions.

This study also reflects that age is an important factor determining the cause of anaemia. Malignancy particularly of gastrointestinal tract origin contributing to anaemia was found in middle aged people 46 years and above whereas haematological causes or other systemic illness or no identified cause was found in younger people between 15 to 45 years. Some earlier studies have found evidence of such differences<sup>8</sup>. So investigations for anaemia should be tailored to the patient's age and the clinical setting.

The sensitivities and specificities of symptoms show that these are not good indicators of the likely site of

a lesion causing anaemia. Although site specific symptoms were associated with site specific lesions, the absence of symptoms did not exclude the possibility of detecting a lesion at a particular site. 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.

Even after extensive investigation the cause of anaemia may remain elusive in a small proportion of cases. This group of patients is difficult to manage, careful follow up with symptomatic treatment and if necessary repetition of investigation is required for them.

This study was conducted on a selected group of patients presenting to a specialized unit of a tertiary care hospital. The sample size was also small. Despite these limitations, findings of this study generally indicate the various types of underlying diseases in patients with anaemia and gastrointestinal symptoms.

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