

Review Article

Anaemia in Alimentary Tract Disease

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Blood loss from the alimentary tract may be chronic and occult resulting in anaemia, or, acute requiring emergency resuscitation, investigation and management. Anaemia in alimentary tract disease usually results from deficiency of iron, vitamin B₁₂ or folic acid. In this review, the common causes of chronic anaemia manifesting in the alimentary tract are discussed. The importance of clinically diagnosing and treating the underlying disease is emphasized.

Keywords: Bleeding; Chronic; Anaemia; Disease; Alimentary tract

Introduction

Anaemia may be the result of blood loss due to a number of causes in the gastrointestinal tract. The loss can be obvious and spectacular as in bleeding oesophageal varices, peptic ulcer, or insidious and occult from a colonic polyp. Anaemia can also be due to malabsorption of iron, folate, and vitamin B₁₂ because of a variety of disease, or can simply reflect an inadequate dietary intake through illness, alcoholism, depression. Chronic or occult bleeding may occur from any part of the gut causing iron-deficiency anaemia [1,2]. Other causes of anaemia occasionally encountered for example, the normocytic normochromic anaemia from bone marrow depression of chronic disorders such as malignancy, the functional iron deficiency in chronic inflammatory diseases (e.g. rheumatoid arthritis, inflammatory bowel disease), the autoimmune hemolytic anaemia associated with ulcerative colitis and the tuberculosis of the small intestine and the sideroblastic anaemias which are genetic or acquired disorders characterized by dyserythropoiesis and iron overload will not be discussed. When the type of anaemia has been determined as a result of examination of the blood, the diagnosis of the underlying cause must always be sought (Table 1) [2-4].

Discussion

Bleeding from the gastrointestinal tract

Chronic gastrointestinal bleeding can occur in recurrent overt blood loss (hematochezia, melaena or hematemesis) or as occult gastrointestinal bleeding [5]. Melaena is the black and tarry faecal output from the anus following a bleed from the upper gastrointestinal tract (oesophagus down to the right side of the colon). The bleeding has to be slow enough to allow the blood time to be chemically altered during its transit through the bowel. The exception to this is the acute torrential bleeding from an upper gastrointestinal source, where the blood can rush through the bowel and manifest as bright rectal bleeding. In these cases the patient is usually ill with a tachycardia and low blood pressure and will need urgent intervention [6]. In the other extreme, patients with gastroduodenal bleeding of up to 100ml per day may have normal appearing stools [7]. This occult bleeding from the gastrointestinal tract is typically identified by either a positive stool test for occult blood [8], or by the presence of iron-deficiency anaemia [2,3,9]. About 5% of all patients with gastrointestinal bleeding do not have lesions identified by upper or lower gastrointestinal endoscopy. In most of these patients the bleeding source responsible for the

chronic blood loss is located in the small bowel [1,2-4,7,9].

Iron-deficiency anaemia

Although the major cause of iron deficiency anaemia is blood loss from the alimentary tract, in women menstrual blood loss must also be considered. In some cases of chronic and occult blood loss the patient may present with symptoms of anaemia, such as, dyspnoea, dizziness, or angina. In chronic iron deficiency, papillary atrophy of the tongue, atrophy of the buccal mucosa, angular stomatitis, koilonychias, and oesophageal webs are all well-known features, but severe iron deficiency may exist with none of these clinical pointers [3,5,9]. The diagnosis is, however, usually readily apparent on routine examination of the blood. The lower the hemoglobin the more likely there is to be serious underlying pathology and the more urgent is the need for investigation. A reduced hemoglobin level is associated with a microcytic low Mean Corpuscular Volume (MCV), below 75fl, and a hypochromic low Mean Corpuscular Hemoglobin (MCH), below 27pg; the blood film reveals microcytic hypochromic red cells [2,5,9,10]. Red cell indices provide a sensitive indication of iron deficiency in the absence of chronic disease, B₁₂ and folate deficiency or hemoglobinopathy. Hemoglobin electrophoresis is recommended when microcytosis and hypochromia are present in patients of appropriate ethnic background to prevent unnecessary gastrointestinal (GI) investigation [9]. The serum iron is low and the total iron-binding capacity is raised with a percentage saturation below 16%. Iron stores are absent from the bone marrow, but a better guide to the level of iron stores is the serum ferritin level which is always very low in iron-deficiency anaemia. Thus, serum ferritin is the most powerful test for iron-deficiency. The demonstration of low serum ferritin level will obviate the need for measurement of both serum iron and total iron binding capacity and makes bone marrow examination unnecessary [11-13]. Folate, vitamin B₁₂, albumin tests are required if malabsorption is suspected. Prothrombin time (13-15sec) or ratio (INR) 1.0: 1.1) should be within 30% of normal range before jejunal biopsy [2,9].

Causes of Iron-deficiency anaemia

Bleeding may occur from any part of the alimentary tract and chronic occult blood loss from the gastrointestinal tract is a major cause of iron deficiency anaemia [2-4].

Chronic Bleeding from the Upper gastrointestinal tract

Bleeding from the mouth is seen in hereditary conditions such as

Table 1: Summary of the causes of chronic anaemia in the alimentary tract.

Iron deficiency anaemia	Anaemia caused by Vitamin B12 deficiency	Folate deficiency anaemia
Bleeding from the alimentary tract	Pernicious anaemia	Celiac disease and tropical sprue
Iron loss	gastric surgery	Resection of small intestine
Malabsorption of iron	Stagnant loop syndrome	Prolonged drug therapy
	Crohn's disease and ileal resection	Crohn's disease
	Imerslund's disease	Lymphoma of small bowel
	Fish tapeworm	Amyloidosis
	Tropical sprue and celiac disease	Whipple's disease
		Alcoholism

Hereditary Hemorrhagic Telangiectasia (HHT), which is a Mendelian dominant inheritance. The lesions consist of small pinpoint bright red blebs that blanch on pressure and may be situated on the lips, gums, buccal mucosa, palate, tongue, nasal mucous membrane, lungs and the skin of the fingers. This condition is sometimes associated with arteriovenous malformations lower down the alimentary tract. Although rare, the importance of this condition lies in the fact that these telangiectasia are prone to bleeding and cause epistaxis, gastrointestinal bleeding and haemoptysis [14]. Oesophageal bleeding may result from varices, carcinoma or hiatus hernia. Iron deficiency anaemia, glossitis and oesophageal web (Patterson - Brown- Kelly or Plummer- Vinson syndrome) characterized by dysphagia is a risk factor for squamous cell carcinoma of the middle or upper third of the oesophagus (post cricoid) and responds to iron supplementation treatment [15]. Blood loss from a hiatus hernia occurs in 3-38% of cases [16]. The most frequent complication of gastroduodenal ulcer disease is non-variceal upper GI haemorrhage which accounts for the commonest cause of ulcer-related death. The presentation may vary from melaena to occult haemopositive stools, to massive haemetemesis and shock [6]. Gastric carcinoma should always be borne in mind particularly if associated with mild dyspeptic symptoms, anorexia and weight loss [9]. Duodenal ulcer is the most common cause of bleeding from the duodenum, but carcinoma of the ampulla of Vater should always be considered if iron deficiency is associated with obstructive jaundice [2-4]. The common causes of upper GI haemorrhage (in UK) are listed in Table 2 [6]. The most common cause for gastrointestinal bleeding of small bowel origin is angiodysplasia [17]. tumours of the small intestine (primary benign such as the hamartomatous polyps in the Peutz-Jeghers syndrome, malignant tumours including lymphoma or metastatic lesion). Various other causes such as ulcers caused by NSAIDS, aortoenteric fistula, diverticula, endometriosis and haemobilia. Haemobilia is a condition in which blood from a malformed hepatic artery may escape into the bile ducts and give rise to anaemia. It is a rare but important cause of obscure blood loss from the alimentary tract [18]. Rarely, vascular (arteriovascular) malformations may occur [19]. Angiodysplasia in the gut are more common in the elderly and are susceptible to bleeding. The best investigation to identify them is colonoscopy as they are more common in the colon and the lesions can be cauterized. Rarely, if bleeding is excessive or the lesions extensive, the patient may need resection of the affected bowel [17]. Other causes are Meckel's Diverticulum, particularly in children, Crohn's disease, vascular occlusions, intussusceptions and volvulus [19,20]. Intestinal ischaemia including ischaemic colitis, results in

Table 2: Causes of Upper Gastrointestinal haemorrhage (in UK).

Peptic ulcers/ erosions (45%)
Idiopathic (25%)
Oesophagitis (10%)
Gastro-oesophageal cancer (5%), varices (5%), Mallory-Weiss tear (5%), angiodysplasia, or Dieulafoy ulcer (5%)

intraluminal blood loss and may present with dark blood passed per rectum. Causes include mesenteric arterial or venous infarction or mesenteric embolism. Ischaemia as a result of bowel strangulation or obstruction may result in blood loss, as seen with intussusceptions. Blood loss from the small intestine may be difficult to diagnose. After negative upper and lower endoscopy, examination of the small bowel is necessary. Methods to evaluate the small bowel include enteroscopy, capsule endoscopy, small bowel radiographic studies and angiography [2-4,9]. The role of each examination depends upon the clinical setting and available expertise. Exploratory surgery with intraoperative enteroscopy is generally reserved for patients with ongoing transfusion requirement and in those under the age of 50 years to rule out a small bowel neoplasia [2,9].

Chronic bleeding from the lower gastrointestinal tract

Bleeding from the lower gastrointestinal tract is a common clinical problem (Table 3). It affects people of all ages, though the aetiology varies in different age groups (Table 4) [21]. Although patients are alarmed when they pass blood, most have minor anorectal disorders that can be investigated and treated on the outpatient or day case basis [22]. Haemorrhoids are extremely common but should not be assumed to be the cause of bleeding until more serious conditions such as neoplasms and inflammatory bowel disease have been excluded. Anorectal examination, sigmoidoscopy, colonoscopy, and barium enema examination if colonoscopy is not readily available form the mainstay of diagnosis of minor lower gastrointestinal haemorrhage [23]. A smaller proportion have colorectal neoplasia, or profuse life threatening haemorrhage. Bleeding from the large bowel is usually the result of conditions such as ulcerative colitis, carcinoma, polyps, diverticular disease and ischaemic colitis which are easier to detect by colonoscopy [21]. In addition, more than one cause of rectal bleeding can co-exist. The recently established technique Computed Tomography (CT) colonography (virtual colonoscopy) can detect colon cancer and colonic polyps as small as 3mm [24]. VC comprises two low-dose CT scans of the abdomen and pelvis, and is less invasive than optical colonoscopy, requires no conscious sedation and is better tolerated by patients [24,25]. However, it lacks the facility of

Table 3: Causes of bleeding per rectum.

Anus/ Rectum	Colon	Upper GI tract
Haemorrhoids	Ulcerative colitis	Torrential bleeding
Anal fissure	Crohn's colitis	
Carcinoma rectum	Ischaemic colitis	
	Carcinoma colon	
	Polyps	
	Angiodysplasia	
	Infective colitis	

Table 4: Causes of lower gastrointestinal haemorrhage in different age groups.

Children	Adults	Elderly people
Meckel's diverticulum	Inflammatory bowel disease	Diverticular disease
Juvenile polyps	Adenomatous polyps	Angiodysplasia
Inflammatory bowel disease	Carcinoma	
	Arteriovenous malformations	
	Small intestinal neoplasia	
	Hereditary telangiectasia	
	Infective colitis	
	Haemorrhoids	
	Solitary rectal ulcer	
	Anal fissure	

polyp biopsy or removal.

Common clinical patterns of bleeding in the lower GI tract

The character of blood loss is dependent on the rate of haemorrhage and the site of the source. Patients with brisk haemorrhage and those with distal colorectal lesions tend to pass bright red blood. If the bleeding is slow or the source is in the proximal colon the blood is altered, being darker red in colour, and mixed with faeces. Right-sided colonic lesions may present with occult chronic blood loss with apparently normal unaltered faeces, so much that a patient with a right iliac fossa mass and iron deficiency anemia has caecal carcinoma until proven otherwise [5]. Patients with bleeding haemorrhoids pass bright red streaks of blood, which they initially notice on the faeces, on toilet tissue, or in the toilet bowl. First-degree (non-prolapsing) haemorrhoids are impalpable and present with bleeding only. The diagnosis can be established at proctoscopy, at which time the haemorrhoids can be injected with 3% phenol. Occasionally, bleeding can be vigorous and actually drip from the anal canal. Such bleeding is usually associated with large or prolapsed haemorrhoids, painless and can occur spontaneously. Anal fissure is associated with fresh blood-staining of toilet paper and pain on defaecation [22,23]. Patients with inflammatory bowel disease tend to lose small amounts of blood mixed with mucus and faeces and they usually have increased bowel frequency [26,27]. Abdominal pain with ulcerative colitis may be colicky prior to defaecation and is relieved by the act [26]. Similar symptoms are also seen in patients with irradiation proctocolitis, which usually follows radiotherapy for pelvic malignancy. An obliterative arteritis develops in the irradiated large bowel that causes mucosal ischaemia, ulceration, and bleeding. Chronic blood loss may lead to anaemia necessitating transfusion. Diversionsary

stomas may ease the blood loss temporarily but the condition usually progresses. For severe symptoms and persistent blood loss resection of the diseased rectum is indicated with either a coloanal anastomosis or a permanent colostomy depending on the extent of disease [28]. The common presenting symptom of patients with distal colorectal polyps and cancers is the passage of red or slightly altered streaks of blood. If the tumour is in the proximal colon the blood lost is darker in colour, and less obvious [29]. Bleeding in patients with colonic diverticular disease and colonic angiodysplasia is often brisk, causing a sudden urge to defaecate, followed by the passage of a large dark red stool. This may be repeated but the bleeding usually stops spontaneously, although the bleeding may be sufficient to cause life threatening hypovolaemic shock [30,31]. Severe haemorrhage occasionally develops in patients with solitary rectal ulcer [32]. Patients with ischaemic colitis are usually elderly and present with fairly sudden onset of left sided abdominal pain associated with blood-stained diarrhea [33]. Most cases occur spontaneously but it is also seen in a small number of patients after aortic surgery and in patients with occlusive atheromatous disease or embolism affecting the flexure watershed between the superior mesenteric artery supply and the inferior mesenteric artery supply [33,34].

Iron loss

Ninety percent of the total cell loss from the gut is from the small intestine which is roughly equivalent to 250g of cells per day [35]. The cell loss from the stomach is also very large and, as in the small intestine, results from a prodigious cell turnover. Each desquamated cell from the stomach and small intestine carries with it a small amount of ferritin. In the normal individual, much of the ferritin is probably broken down and the iron reabsorbed, but in conditions such as chronic atrophic gastritis and celiac disease the cell turnover is greatly increased and the iron losses are increased proportionately [35-37]. Moreover, in coeliac disease it is probable that less of the desquamated iron is reabsorbed and results in a significant loss of iron from the body [37,38]. Excretion of iron in the bile does not seem to be an important source of iron loss [35].

Malabsorption of iron

Iron-deficiency anaemia may accompany chronic atrophic gastritis [36]. These patients usually have total achlorhydria and frequently have circulating parietal cell antibody in the peripheral blood, perhaps because the gastritis is of autoimmune origin. Achlorhydria is associated with impaired absorption of inorganic iron, although haem iron is absorbed normally [35,36]. In unexplained anaemia the finding of parietal cell antibody in peripheral blood may be significant. [2,36]. Iron-deficiency anaemia is present in 40% to 50% of patients following gastrectomy [39]. Impaired absorption of food iron and impaired dietary intake are thought to be contributory factors [40]. Iron absorption is also impaired in celiac disease, but the iron deficiency is probably multifactorial and associated in addition with iron loss [37,38]. Iron supplementation correct anaemia and replenish body stores. Normalization of haemoglobin typically occurs after 8 weeks in most patients. True intolerance to oral iron, inflammatory conditions of the bowel, and refusal of the patient to take the tablets are indications for parenteral iron therapy. Prompt and effective iron replacement is needed before urgent surgery and intravenous iron is a likely cost-effective solution that may obviate the

need for blood transfusion [9]. Blood transfusion should be reserved for patients with or at risk of cardiovascular instability due to the degree of anemia [9,41].

Diagnosis of the underlying cause of iron deficiency anaemia

Anaemia is a common condition in adults 60 years and older [42]. Unless there is some very obvious cause, such as dietary deficiency or menorrhagia in pre-menopausal women, bleeding from the alimentary tract should be considered as the cause until proved otherwise. Diagnosis of the underlying cause is all important. It is imperative to take a careful history, noting anorexia, weight loss, dyspepsia or a change of bowel habit. An enquiry about the ingestion of salicylates or NSAIDs should be made and a family history will be helpful in uncovering inherited bleeding disorders. On clinical examination, petechial haemorrhages, bruising or telengectasia should be excluded. Abdominal masses may be present or there may be signs of liver disease such as spider naevi and palmar erythema. Digital examination of the rectum and proctoscopy/sigmoidoscopy and +/- biopsy are mandatory. A suitable FOB test is one that will give a definite positive when the patient is losing 10ml blood or more per day in the stool. A positive result in two or more specimens indicates bleeding from the alimentary tract. However, if all results are negative it does not exclude such a possibility because the bleeding may be intermittent. These would explain why FOB test may not be of benefit in the investigation of iron deficiency anaemia [9]. Upper gastrointestinal endoscopy is preferable to a barium meal, because biopsies can be taken. Low duodenal biopsies should always be taken to exclude celiac disease at an early stage if the endoscopy does not reveal the cause of iron deficiency. It is convenient to perform colonoscopy immediately after upper gastrointestinal endoscopy, under the same sedation [43]. In patients > 50 or with marked anaemia or a significant family history of colorectal cancer, lower GI investigation should still be considered even if celiac disease is found [9]. Colonoscopy allows biopsies to be taken of any colonic lesions and the cause to be treated if bleeding is due to polyps or angiodysplasia. Only if colonoscopy is not readily available that barium enema is performed. This is because patients will be subjected to a further procedure (colonoscopy and polypectomy) should polyps be detected. Good views of the caecum are important in colonoscopy or barium enema x-ray to exclude a neoplasm. The elderly, frail patient with weight loss may benefit from an initial unprepared (bowel preparation may be risky) CT scan of the abdomen, pelvis and thorax, and, if malignancy is found, endoscopy may not be necessary (Table 5) [2,9].

Further investigations

If the cause of iron deficiency anaemia has not been diagnosed after the investigations above, it is wise to retake the history and review the results, to ensure that obvious causes (dietary insufficiency, menstrual loss) or haemoglobinopathy have not been overlooked [2,9]. For patients who are asymptomatic, it is reasonable to stop iron therapy and to repeat the full blood count after 3-6 months; if anaemia recurs, then further investigation is warranted. For symptomatic patients, those needing repeat transfusions, or in whom there is clear evidence of gastrointestinal blood loss (recurrent rectal bleeding, or positive faecal occult blood), then the following investigations are suggested: Colonoscopy with good preparation is essential if angiodysplasia or telangiectasia are to be seen, usually in the ileocaecal region.

Table 5: Management of minor lower gastrointestinal haemorrhage.

Management of minor lower gastrointestinal haemorrhage	
1.	History and general examination
2.	Anorectal examination
3.	Proctosigmoidoscopy
4.	Colonoscopy or Double contrast barium enema examination
5.	Treatment of cause

Small bowel radiology is useful in Crohn's disease which is usually associated with a high platelet count and raised ESR, but occasionally presents with iron deficiency and weight loss especially in adults [2,9]. Bone marrow smear would exclude sideroblastic anaemia, after discussion with the haematologist. 51 Cr- labeled red cell scan would elucidate chronic blood loss which is occasionally located to one region of the intestine (proximal or distal colon or small intestine). Careful colonoscopy, or surgery and operative endoscopy may then be indicated to identify the vascular malformation that usually causes the bleeding [7]. Meckel's diverticulum scan may detect bleeding from ulcerated, heterotopic gastric tissue which rarely causes anaemia in adolescents or adults. A diverticulum may also be visible on small bowel radiology. Laparotomy is rarely helpful unless there are clues to the source of blood loss beforehand [7]. Thus, referral to a specialist centre is advisable before a 'blind' laparotomy [9].

Anemia caused by vitamin B₁₂ deficiency

Megaloblastic anaemia and the sequelae of neurological degeneration of the spinal cord white matter results from altered DNA synthesis of all blood cells, usually resulting from vitamin B and or folic acid deficiencies [2,9]. Vitamin B₁₂ is found in animal foods, mainly meat. In the gut lumen, vitamin B₁₂ initially combines with an R binder to form the R binder complex. This is broken down by pancreatic proteases to liberate B₁₂, which then binds with Intrinsic Factor (IF), a glycoprotein with a molecular weight of over 44 000 found in gastric juice, being secreted by the parietal cells of the body and fundus of the stomach. Vitamin B₁₂-IF complex is attached to specific receptors situated on the membrane of the microvilli of the mucosal cells of the lower part of the ileum. The vitamin B₁₂ makes its way to the mitochondria of the enterocyte where it remains for some hours, but IF remains in the lumen. B₁₂ is then transported from the enterocytes by the glycoprotein Transcobalamin II (TC II) to the marrow, but the transport mechanism into the serum is not clearly understood. In serum, B₁₂ is mainly bound to TC I (70-90%) and some to TC III (<10%), but neither protein plays a role in delivering B₁₂ to the marrow. TC I and TC III are derived from granulocytes and thus a rise in serum B₁₂ is seen in myeloproliferative disorders. Vitamin B₁₂ deficiency gives rise to megaloblastic anaemia which may be associated with a red, atrophic and painful tongue [44] with angular stomatitis and in some cases, splenomegaly. As in iron deficiency, however, such clinical findings may be absent [45, 46]. Examination of the blood shows a macrocytic anemia with oval macrocytes on the blood film and a high MCV (above 100fl) and a normal MCH. This type of anaemia is not infrequently associated with neutropenia and thrombocytopenia and, in addition to the presence of oval macrocytes, the blood film may also show hypersegmented polymorphs. A bone marrow smear is usually necessary for the confirmation of the diagnosis, by the demonstration of megaloblasts

and giant metamyelocytes. The serum B₁₂ level is low (below 135pg/ml). B₁₂ deficiency is almost always due to impaired absorption as a result of disease of the stomach (pernicious anaemia) or the small intestine [46]. Thus, a satisfactory test of the extent of absorption depends on measuring urinary excretion after giving 57 Co-labelled B₁₂ (Schilling test) [47]. 57 Co-labelled B₁₂ (1.0ug) is given by mouth at the same time a larger dose (1mg) of unlabelled B₁₂ is given intramuscularly. This large dose of unlabelled B₁₂ overburdens the binding capacity of the protein responsible for B₁₂ transport in the plasma and this results in the urinary excretion in the 24 hours following administration of about one-third of the 57 Co-B₁₂ that is absorbed. In normals, 10% or more of the administered dose is excreted. Values below may be taken as evidence of defective absorption. In pernicious anaemia it is usual to find values below 5%. If a second test is carried out with the addition of intrinsic factor, a differentiation can be made between pernicious anaemia and small bowel or pancreatic disease (steatorrhoea) since with the former B₁₂ absorption will return to near normal levels whereas in the latter B₁₂ absorption will remain low. If the impaired absorption is not corrected by IF, then the disease lies in the small intestine and the elucidation of the exact cause may require careful radiology of the small intestine together with other investigations such as jejunal biopsy and absorption tests. If the urine specimens are not collected correctly and renal function is not good, a whole body counting apparatus gives a much more reliable measurement of the absorption of B₁₂ and should be used whenever possible [9]. Occasionally, it is possible to demonstrate correction of the impaired absorption following a course of antibiotics (tetracycline), and this indicates the stagnant loop syndrome causing bacterial overgrowth, but the exact cause of this will depend on further investigation of the alimentary tract [47]. Dietary deficiency of vitamin B₁₂ may occur in very strict vegetarians (vegans) who eat no meat or animal products in their diet. Vitamin B₁₂ therapy consists of Neo-Cytamen (1000 micrograms twice a week for the initial few weeks) in order to replenish body stores followed by 1000 micrograms every 1-2 months [9].

Pernicious anaemia

The cardinal features of pernicious anaemia are chronic atrophic gastritis, achlorhydria and impaired secretion of Intrinsic Factor (IF) [48]. Circulating parietal cell antibody is detectable in 80% - 90% of cases and circulating IF antibody in 60%-70%. It is a disease of older age groups and usually occurs over the age of 40 years. It may very occasionally be seen in younger patients. Some children develop juvenile pernicious anemia because they have the ability to secrete hydrochloric acid, but their parietal cells do not secrete intrinsic factor. Other children secrete intrinsic factor that is abnormal in both structure and function and therefore results in impaired absorption of vitamin B₁₂ [2,48].

Gastric surgery

Gastric surgery occasionally results in vitamin B₁₂ deficiency. It is always seen following total gastrectomy and in about 50% of those patients who undergo partial gastrectomy [39]. It usually takes some years to develop because of the large body stores of the vitamin [39,40].

Stagnant loop syndrome

The stagnant loop syndrome arises as a consequence of anatomical

abnormalities of the small bowel, strictures, anastomoses and blind loops. It may also be seen in patients who have interference with gut motility, as in scleroderma. These disease states results in bacteria overgrowth in the jejunum, the results of which are complex but malabsorption of fat and vitamin B₁₂ is usually present [49]. A course of broad spectrum antibiotics such as tetracycline will usually restore vitamin B₁₂ absorption to normal, but only temporarily, and complete cure may require surgery [40,49,50].

Crohn's disease and ileal resection

Megaloblastic anaemia occurs in about 20% of patients with enterocolitis and is usually caused by disease of the lower ileum or bypass operations that divert the contents of the small intestine from this part of the bowel, thus interfering with intestinal absorption of vitamin B₁₂. Resection of as little as 1.5-2m of the terminal ileum may have the same effect. Crohn's disease occasionally gives rise to the stagnant loop syndrome [49].

Imlerslund's disease

Imlerslund's disease consists of specific malabsorption of vitamin B₁₂, proteinuria and megaloblastic anaemia. It is a rare autosomal recessive disease of the small bowel and the commonest cause of vitamin B₁₂ deficiency in children [51]. It responds to parenteral vitamin B₁₂ therapy.

Fish tapeworm

The fish tapeworm (*Diphyllobothrium latum*) competes with the human host for vitamin B₁₂. In Nordic countries, megaloblastic anaemia secondary to diphyllobothriasis has been reported [52]. The worm finds its way into man through inadequately cooked fish that contain larvae in their muscle. The worms develop in the ileal region where they compete for vitamin B₁₂. Oral or parenteral vitamin B₁₂ administration after parasite expulsion with antihelminthics brings levels back to reference range [52].

Folate deficiency anaemia

Folate deficiency is indistinguishable from vitamin B₁₂ deficiency on clinical grounds except that it occurs in all age groups, unlike pernicious anaemia, which is more frequent in the older age groups [42]. The changes in the peripheral blood and bone marrow are identical to those seen in vitamin B₁₂ deficiency, except both the serum folate level and the red cell folate level is low [54]. Folic acid is absorbed from the jejunum and therefore when folic acid deficiency is caused by disease of the alimentary tract the disease usually lies in this area. As celiac disease is the most common cause of folate deficiency in the UK, jejunal biopsy and other absorption studies may be required together with careful radiology [37]. More than 90% of celiac disease and tropical sprue patients have malabsorption of folate from progressive villous atrophy of the small intestine and many of them present with megaloblastic anaemia. Dermatitis herpetiformis is often associated with changes in small intestine that are indistinguishable from celiac disease, but the severity of both mucosal damage and the folate deficiency tends to be less. Impaired absorption of other vitamins, minerals, glucose, fat and protein may be demonstrated, and radiological examination will show flocculation of the barium and variation off the caliber of the small intestine.

Extensive resection of the jejunum is an uncommon complication of surgery, and, although the resulting malabsorption is usually mild

it does not usually present great diagnostic difficulty. However, lymphoma, amyloidosis and some of the other rarer causes may require investigation in specialist units before the diagnosis becomes apparent. Dietary deficiency of folate is seen much more frequently than dietary deficiency of vitamin B₁₂. There are two factors contributing to this: the body stores of folate are much less in relation to the needs, and much of the food folate is destroyed in cooking. An inadequate diet, even for a few months may result in folate deficiency. Folic acid therapy consists of a 5mg tablet twice daily by mouth [45,46].

Tropical sprue and coeliac disease

Tropical sprue and coeliac disease are primarily malabsorptive states that are associated with vitamin B₁₂ deficiency in about 40% of patients [37,53]. Tropical sprue is post-infective tropical malabsorption that affects adults of any race who have lived in India, Asia or Central America, but is rare in Africa. It usually follows an acute attack of diarrhoea but the cause of mucosal damage is uncertain although secondary bacterial overgrowth and hypolactasia commonly exacerbate the malabsorption. Treatment of tropical sprue is with broad-spectrum antibiotics such as tetracycline which normalizes mucosal structure and resolve malabsorption [53]. Folate and B₁₂ replacement cures the macrocytic anaemia and the accompanying glossitis but may not restore villous atrophy and malabsorption usually persists. Coeliac disease is treated by putting the patient on a gluten-free diet and appropriate replacement therapy of substances in which the patient is deficient as a result of malabsorption [37].

Prolonged drug therapy

Prolonged therapy with some anticonvulsants, such as phenytoin, primidone and barbiturates, may cause megaloblastic anaemia. Impaired malabsorption has also been attributed to the contraceptive pill, but evidence that megaloblastic anaemia as a result of either group of drugs, is caused by impaired absorption alone is inconclusive. It is more probably multifactorial and other factors such as inadequate nutrition may be contributory. Other less common causes of folic malabsorption include Crohn's disease, lymphoma of the small bowel, amyloidosis and alcoholism [45].

Conclusions

Anemia caused by alimentary tract disease usually results from deficiency of iron, vitamin B₁₂ or folic acid. Chronic or occult bleeding may occur from any part of the gut causing iron-deficiency anaemia. When the type of anaemia has been determined as a result of examination of the blood, the diagnosis and treatment of the underlying cause must always be sought.

References

- Rockey DC. Occult gastrointestinal bleeding. *Gastroenterol Clin North Am.* 2005; 34: 699-718.
- Elli L, Norsa L, Zullo A, Antonio Carroccio, Carlo Girelli, Salvatore Oliva, et al. Diagnosis of chronic anaemia in gastrointestinal disorders: A guideline by the Italian Association of Hospital Gastroenterologists and Endoscopists (AIGO) and the Italian Society of Paediatric Gastroenterology Hepatology and Nutrition (SIGENP). *Dig Liver Dis.* 2019.
- Bampton PA, Holloway RH. A prospective study of the gastroenterological causes of iron deficiency anaemia in a general hospital. *Aust NZ J Med.* 1996; 26: 793-799.
- Lopez RA, Camacho G F, Calderon G C, Miño Fugarolas G. Iron deficiency anaemia due to chronic gastrointestinal bleeding. *Rev Esp Enferm Dig.* 1999; 91: 345-358.
- Wilson ID. Hematemesis, melaena, and hematochezia. In: Wilker HK, Hall WD, Hurst JW, editors. *Clinical Methods: The History, Physical, and Laboratory Examinations* 3rd edition. Boston: Butterworths. 1990.
- Rockall TA, Logan RF, Devlin HB, Northfield TC. Risk assessment after acute upper gastrointestinal haemorrhage. *Gut.* 1996; 38: 316-321.
- Orlandi M, Inano W. Chronic gastrointestinal bleeding. *Ther Umich.* 2006; 63: 327-332.
- Kronborg O. Faecal occult blood tests in adenoma detection. *Eur J Cancer Prev.* 1993; 2: 107-110.
- Goddard AF, James MW, McIntyre AS, Scott BB, British Society of Gastroenterology. Guidelines for the management of iron deficiency anaemia. *Gut.* 2011; 60: 1309-1316.
- Guyatt GH, Oxman AD, Ali M, Willan A, McIlroy W, Patterson C. Laboratory diagnosis of iron-deficiency anaemia: an overview. *J Gen Intern Med.* 1992; 7: 145-153.
- Baicus C, Cariola S, Rimbasi M, Patrascu R, Baicus A, for Grupul de Studiu al Scaderii Ponderale Involuntare. Utility of routine hematological and inflammation parameters of the diagnosis of cancer in involuntary weight loss. *J investing Med.* 2011; 59: 951-955.
- Biacus C, Cariola S, Rimbasi M, Patrascu R, Baicus A, GSSPI. Ferritin above 100mcg/l could rule out colon cancer, but not gastric or rectal cancer in patients with involuntary weight loss. *BMC Gastroenterol.* 2013; 12: 86.
- Kishida T, Schinozawa I, Tanaka S, Hoshino T, Tatsuguchi A, Feng L. Significance of serum iron and ferritin in patients with colorectal adenomas. *Scand J Gastroenterol.* 1997; 32: 233-237.
- Gonzalez CD, Cipriano SD, Topham CA, Stevenson DA, Whitehead KJ, Vanderhooft S, et al. localization and age distribution of telangiectasases in children and adolescents with hereditary hemorrhagic telangiectasia: A retrospective cohort study. *J Am Acad Dermatol.* 2019.
- Goel A, Bakshi SS, Soni N, Chhavi N. Iron- deficiency anaemia and Plummer-Vinson syndrome: current insights. *J Blood Med.* 2017; 8: 175-184.
- Panzuto F, di Giulio E, Capurso G, Baccini F, D'Ambra G, Delle Fave G, et al. large hiatal hernia in patients with iron deficiency anaemia: a prospective study on prevalence and treatment. *Aliment pharmacol Ther.* 2004; 19: 663-670.
- Soran H, Lewis M, Whrwell PJ. Bleeding angiodysplasia: should we concentrate more on the aortic valve than on the bowel? *Int J Clin Pract.* 2002; 56: 155-156.
- Menaria P, Mudana V. Hemobilia arteriohepatic fistula. *Oxf Med Case Reports.* 2019; 20.
- Maddah G, Abdollahi A, Roubakhsfar O, Taraz Jamshidi S, Hassanpour M. Arteriovenous malformations of the colon: A report of two cases and review of the literature. *Caspian J Intern Med.* 2017; 8: 52-55.
- Contaldo A, Losurdo G, Albano F, Iannone A, Barone M, Ierardi E, et al. The spectrum of small intestinal lesions in patients with unexplained iron deficiency anaemia detected by video capsule endoscopy. *Medicina (Kaunas).* 2019; 55: 3.
- Zuccaro G. Epidemiology of lower gastrointestinal bleeding. *Best Pract Res Clin Gastroenterol.* 2008; 22: 225-232.
- Weledji EP. Minor anorectal conditions in proctology. *Austin J of Surgery.* 2018; 5: 1143.
- Fargo MV, Latimer KM. Evaluation and management of common anorectal conditions. *Am Fam Physician.* 2012; 85: 624-630.
- Burling D, Taylor SA, Halligan S. Virtual colonoscopy; current status and future directions. *Gastrointest Endosc Clin North Am.* 2005; 15: 773-795.
- Halligan S, Taylor SA. CT colonography: results and limitations. *Eur J Radiol.* 2007; 61: 400-408.

26. Barnert J, Messmann H. Management of lower gastrointestinal tract bleeding. *Best Pract Res Clin Gastroenterol*. 2008; 22: 295-312.
27. Daperno M, Sostegni R, Rocca R. Lower gastrointestinal bleeding in Crohn's disease: How (un)common is it and how to tackle it? *Dig Liver Dis*. 2012; 44: 721-722.
28. Do NL, Naglev D, Poylin VY. Radiation Proctitis: Current strategies in Management. *Gastroenterology Research and Practice*. 2011; 2011.
29. Wauters H, van Casteren V. Rectal bleeding and colorectal cancer in general practice: diagnostic study. *BMJ*. 2000; 321: 988-999.
30. Adams JB, Margolin DA. Management of Diverticular haemorrhage. *Clinics in Colon and Rectal Surgery*. 2009; 22: 181-185.
31. Athanasoulis CA, Galdabini JJ, Waltman AC, Novelline RA, Greenfield AJ, Ezpeleta ML. Andiodysplasia of the colon: a cause of rectal bleeding. *Cardiovasc Radiol*. 1978; 1: 3-13.
32. Komai T, Omata F, Shiratori Y, Kobayashi D, Arioka H. Risk factors for acute hemorrhagic rectal ulcer syndrome and its prognosis: a density case-control study. *Gastroentero Res Pract*. 2018; 2018.
33. Uchida T, Matsushima M, Oribashi Y, Dekiden-Monma M, Mizukami H, Nakahara F, et al. A case-control study on the risk factors for ischemic colitis. *Tokai J exp Clin Med*. 2018; 43: 111-116.
34. Griffith D. Surgical anatomy of the blood supply of the distal colon. *Ann R Coll Surg Engl*. 1956; 19: 241-256.
35. Munoz M, Villar I, Garcia-Erce JA. An update of iron physiology. *World J of Gastroenterology*. 2009; 15: 4617-4626.
36. Dai Y, Tang Z, Zhang Y. How to assess the severity of atrophic gastritis. *World J Gastroenterol*. 2011; 17: 1690-1693.
37. Green PR, Cellier C. Celiac disease. *N. Engl. J. Med*. 2007; 357: 1731-1743.
38. Barry N, Basha J, Varma N, Varma S, Prasad KK, Vaiphei K, et al. Anaemia in celiac disease is multifactorial in etiology: A prospective study from India. *JGH Open*. 2018; 2: 5.
39. Kirk RM, Stoddart CJ. Complications of surgery of the upper gastrointestinal tract. London: Bailliere Tindall. 1986.
40. Weledji EP. Overview of gastric bypass surgery. *Int J Surg Open*. 2016; 5: 11-19.
41. Grooteman KV, van Geenan EJM, Kievit W, Dreiden PH. Chronic anaemia due to gastrointestinal bleeding: When do gastroenterologists transfuse? *United European Gastroenterol J*. 2017; 5: 967-973.
42. Lanier JB, Park J, Callahan RC. Anaemia in older adults. *Am Fam Physician*. 2018; 98: 437-442.
43. Hardwick RH, Armstrong CP. Synchronous upper and lower gastrointestinal endoscopy is an effective method of investigating iron-deficiency anaemia. *Br J Surg*. 1997; 84: 1725-1728.
44. Nimi N, Mori N. Papillary atrophy of the tongue. *Clinical Case Reports*. 2018; 6: 2283-2284.
45. Aslinia F, Mazza J, Yale SH. Megaloblastic anaemia and other causes of macrocytosis. *Clin Med Res*. 2006; 4: 236-241.
46. Hoffbrand V, Provan D. ABC of clinical haematology: macrocytic anaemias. *BMJ*. 1997; 314: 430-443.
47. Brigden ML. Schilling test still useful in pernicious anaemia? *Postgraduate Medicine*. 1999; 106: 37-38.
48. Massirini S, Zilli A, Elvevi A, Invernizzi P. The changing face of chronic autoimmune atrophic gastritis: an updated comprehensive perspective. *Autoimmune Rev*. 2019; 18: 2215-2222.
49. Wegand K, Herfarth C, Weigand K. Stagnant loop syndrome: a rare cause of severe malabsorption. *Visceral Medicine*. 2013; 29: 190-194.
50. King CE, Toskes PP. Bacterial overgrowth syndromes: In Beck JE (ed) *Bockus gastroenterology*. Philadelphia, Saunders. 1985; 1781-1791.
51. Broides A, Yerushalami B, Levy R, Hadad N, Kaplun N, Tanner SM, et al. Imerslund-Grasbeck syndrome associated with recurrent aphthous stomatitis and defective neutrophil function. *J.Pediatr hematol Oncol*. 2006; 28: 715-719.
52. Nyberg W, Grasbeck R, Saarni M, et al. Serum vitamin B₁₂ levels and incidence of tapeworm anemia in a population heavily infected with *Diphyllobothrium latum*. *Am J Clin Nutr*. 1961; 9: 606-612.
53. Westergaard H. Tropical Sprue. *Curr Treat Options Gastroenterol*. 2004; 7: 7-11.
54. Snow CF. Laboratory diagnosis of vitamin B₁₂ and folate deficiency: a guide for the primary care physician. *Arch Intern Med*. 1999; 159: 1289-1298.