

REVIEW

THE EPIDEMIOLOGY AND THE NOSOLOGY OF OBSCURE GASTROINTESTINAL BLEEDING

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SUMMARY

Obscure gastrointestinal bleeding is defined as persistent and recurrent gastrointestinal bleeding, the etiology of which remains unspecified after a first standard evaluation (upper endoscopy, colonoscopy and small intestine specific radiological investigations). This pathology is both a diagnosis challenge (due to the limited possibilities of endoscopic techniques / usual imagistics to properly view the small intestine) and a therapeutic challenge (because of the associated morbidity and mortality), implying a higher consumption of health resources (it requires successive hospitalizations, expensive investigations and repeated transfusions). Most commonly, the bleeding headquarters is located in the small intestine and it is represented by vascular lesions (angiodysplasias), along with inflammatory bowel diseases, tumors and lesions induced by drugs (NSAIDs). In recent years, we have developed advanced diagnosis techniques (Video capsule endoscopy, double-balloon enteroscopy and enterography CT), which had led to a better understanding of the etiologic profile of the obscure gastrointestinal bleeding, allowing the establishment of specific and effective therapies.

Key words: gastrointestinal bleeding, diagnosis, endoscopic techniques

RÉSUMÉ

L'épidémiologie et la nosologie du saignement gastro-intestinal obscur

La saignement gastro-intestinal obscur est défini comme une hémorragie persistante et récurrente, d'étiologie inconnue après une première norme d'évaluation (endoscopie haute, colonoscopie et investigations radiologiques spécifiques du grêle). Cette pathologie est à la fois un défi du diagnostic (en raison des possibilités limitées des techniques endoscopiques usuelles pour visualiser correctement le grêle) et un défi thérapeutique (en raison de la morbidité et la mortalité associées), qui implique une consommation plus grande de ressources de santé (elle demande des hospitalisations successives, des investigations coûteuses et des transfusions répétées). Le plus souvent, le siège du saignement se trouve dans l'intestin grêle et est représenté par des lésions vasculaires (angiodysplasies), ainsi que des maladies inflammatoires de l'intestin, tumeurs et lésions induites par des médicaments (AINS). Au cours des dernières années, nous avons développé des techniques avancées de diagnostic (endoscopie vidéo par capsule, entéroscopie à double ballonnet et entérographie TC), qui ont conduit à une meilleure compréhension du profil étiologique de l'hémorragie digestive obscur, permettant la mise en place de thérapies spécifiques et efficaces.

Mots clés: hémorragie gastro-intestinale, diagnostic, techniques endoscopiques

INTRODUCTION

Gastrointestinal bleeding is one of the major concerns of gastroenterologists in terms of diagnostic, therapeutic and, not least, economic costs [1].

For many years, gastrointestinal bleeding was considered a self-reliant pathology; subsequently, due to progress in the endoscopic and imagistic areas, it was revealed as a dramatic manifestation of an impressive number of diseases (cardiovascular, renal, autoimmune, hematological), that may be expressed in this way. With about 5% of the patients

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with recurrent gastrointestinal bleeding, the bleeding source remains unidentified after routine endoscopic procedures, calling for the definition of a new notion, the one of obscure gastrointestinal bleeding [2]. The etiology which underlies the obscure bleeding remain uncertain in many cases, despite extensive evaluation, leading to recurrent hospitalizations and the need for repeated transfusion administration.

Classification of gastrointestinal bleeding

Gastrointestinal bleeding is bleeding coming from any digestive segment located between pharyngeal and oesophageal junction and anus. Depending on the rate of blood loss, gastrointestinal bleeding can occur in many clinical forms and it can be classified as pieces of evidence (acute) or occult (chronic) [3].

A. Acute or obvious gastrointestinal bleeding is visible as hematemesis, melena or hematochezia

Haematochezia is the loss of fresh blood by excrements, which can come from any digestive level. About 15% of rectal bleedings are gastrointestinal bleedings (the rapid loss of a litre of blood in the upper digestive tract causes red blood excrements) and it is associated with a poor prognosis [4].

Melena is the externalization of the blood by excrements as black stool soft glossy excrements (upon conversion of the hemoglobin into hematin). Melena means the minimum acute loss of 60-80 ml of blood from the upper digestive tract, at a transit of at least 8 hours. The characteristics of the melena also depend on the amount and intensity of bleeding.

Rectoragia represents blood elimination from a rectal cause. Erroneously, all blood losses are called rectoragias, although the headquarters of bleeding may be located almost anywhere in the digestive tract.

Other terms with diagnose relevance encountered in the terminology involving acute gastrointestinal bleeding are listed below.

Recurrent haemorrhage is the reappearance of haematemesis and / or of melena after a period of more than 24 hours of stable vital signs, installing hemorrhagic shock (significant decrease in systolic blood pressure < 100 mmHg increase $\Delta V > 100$ / minute), hemoglobin decrease (by more than 2 g / dl in 24h) and hematocrit [5].

Self-limited acute bleeding refers to active bleeding cease with hemodynamic stability, with no further evidence of bleeding continuance

B. Chronic occult gastrointestinal bleedings

Chronic occult gastrointestinal bleedings are not clinically obvious and they usually appear as iron deficiency anemia, or after a positive occult excrement test.

The epidemiology of gastrointestinal bleeding

The Statistical estimation of gastrointestinal bleeding can be very laborious and it largely depends on the population studied, on the ways of the patient's addressing to the doctor, on the geographical area in which the analysis is

done, on the socio-economic conditions of each country, region or even of each hospital considered.

A. Acute gastrointestinal bleeding

Acute gastrointestinal bleeding in western countries is a major cause of admission and it is estimated at 300,000 patients annually [6].

Upper gastrointestinal bleeding has an annual incidence ranging from 40-150 in 100,000 persons and a mortality rate of 6% -10% compared to the lower GI bleeding, which has an annual incidence ranging from 20 to 27 episodes / 100,000 people and a mortality rate of 4% -10% [7].

Acute gastrointestinal bleeding is more common in men than in women and its prevalence increases with age [8].

B. Chronic occult gastrointestinal bleedings

The incidence of occult bleeding is probably underestimated, since most people are not screened for iron deficiency anemia or fecal occult bleeding. Iron deficiency anemia, as an expression of occult chronic bleeding, is the most common cause of anemia worldwide (about 80% of all anemia). In Western countries, in most cases, iron deficiency anemia is secondary to chronic blood loss [9].

C. Obscure gastrointestinal bleeding - definition / classification

The diagnosis management involves performing upper gastrointestinal endoscopy and colonoscopy, in a first attempt to find the source of bleeding [10]. Approximately 10-20% of the patients with gastrointestinal bleeding, after the initial assessment, do not have an obvious cause of bleeding. Of these, approximately half (5% of all gastro-intestinal bleeding) have recurrent or persistent bleeding, thus posing a real challenge for diagnostic and therapeutic strategy.

Obscure gastrointestinal bleeding is defined as persistent and recurrent gastrointestinal bleeding, undiagnosed, after an initial evaluation consisting of upper gastrointestinal endoscopy and colonoscopy and small bowel specific radiology (Barium) [11].

Obscure gastrointestinal bleeding can be classified according to several parameters.

It is crucial for the clinician to define the type of gastrointestinal bleeding in the clinical picture, considering the diversity of pathologies, which can be complicated with obscure bleeding and the different techniques of approach.

Classification of gastrointestinal obscure hemorrhages depending on blood loss rate : manifest gastrointestinal obscure bleeding, on patients with clinical expressed bleeding (hematemesis, melena and hematochezia); occult gastrointestinal obscure bleeding, documented through positive obscure bleeding stool test with/without iron deficiency anemia.

Depending on the digestive tract segment level of bleeding, gastrointestinal hemorrhages were traditionally classified into: superior (proximal to the ligament of Treitz) or inferior (distal to the ligament of Treitz) [12].

From 2006, following the introduction of new imagistic and endoscopic techniques (endoscopic capsule,

enterography CT), a new classification has been proposed, which the necessary procedures to diagnose and treat the digestive hemorrhage can be decided on: superior gastrointestinal bleeding – the bleeding source is localized proximal to the ampulla of Vater, therefore, accessible to superior endoscopy; medium gastrointestinal bleeding – the lesion is situated between the ampulla of Vater and the ileocecal valve; inferior haemorrhages – a colorectal bleeding source that is approachable by colonoscopy [13].

Most of the patients with obscure gastrointestinal bleeding have the source of bleeding at the small intestine, normally being medium gastrointestinal bleeding. The rest of the lesions are usually in accessible areas to conventional endoscopy, but neglected during prior endoscopy procedures.

Obscure gastrointestinal bleeding epidemiology

Obscure gastrointestinal haemorrhage represents approximately 5% of the gastrointestinal bleeding cases and it proves to be a true challenge for clinicians [14].

The high efficiency of initially missed lesions detection referring to a second endoscopic evaluation (35-75% of patients subjected to superior endoscopy and 6 % of the patients that repeated the colonoscopy) highlights the importance of resuming the endoscopic examinations [15].

Virtually, any type of lesion (vascular, tumor, ulcer and so on) can cause obscure bleeding, and most of these lesions are in the small intestine. The most common cause localized in the small intestine, in Western countries, is angiodysplasia (with a percentage ranging from 20% to 55%), followed by tumors of the small intestine (10% to 20%), Crohn's disease (2% to 10%), celiac disease (from 2% to 5%), Meckel diverticulum (2% to 5%); the enteropathy caused by anti-inflammatory drugs is responsible for about 5%.

Obscure gastrointestinal bleeding-etiology

1. Angiodysplasia

The most common cause of obscure gastrointestinal bleeding is represented by the various vascular abnormalities of the small intestine, the most common being angiodysplasia.

Angiodysplasia (angioectasia or vascular ectasia) is the abnormal tortuous thin walled dilatation, involving veins, arteries and capillaries especially small submucosal and mucosal ones [16]. Most of them are acquired associated with other comorbidities (aortic stenosis, renal failure, ischemic heart disease), but some can be present from birth or as a part of hereditary syndromes [17].

It was ascertained that the most frequent location of angiodysplasia is the cecum and the ascending intestine (78%), while in the jejunum it is found in about 10.5% of the cases, in the ileum 8.5% and in the duodenum 2.3%. [18] About 40-60 % of the patients have more than one lesion located in different parts of the digestive tract [19].

Angiodysplasia located in the small intestine can be responsible for 20-55% of the obscure gastrointestinal bleeding cases.

2. Small intestine tumors

Represent about 5% of all primary neoplasms of the gastrointestinal tract [20]. Small bowel tumors were reported as the second cause of bleeding in the small intestine, representing 10.5% of all patients [21]. The most common primary malignancy is adenocarcinoma of the small intestine, accounting for 35-50%, while 20-40% are carcinoid tumors, lymphomas 14% and sarcomas 11-13% [22].

Adenocarcinomas are more frequently located in the duodenum and proximal jejunum, while lymphomas and carcinoid tumors are located mainly in the distal small intestine, and sarcomas are evenly distributed throughout the small intestine. The most common premises for tumors of the small intestine is the ileum (29.7%), followed by duodenum (25.4%) and jejunum (15.3%) [23].

Benign tumors appear to bleed more often than malignant tumors; the most common benign tumors causing obscure bleeding are leiomyoma, and of malignant tumors, leiomyosarcomas.

3. Crohn's disease

Crohn's disease is a chronic inflammatory idiopathic process that may affect any segment of the digestive tract. It is responsible for 2-10% of the OGIB cases.

The prevalence of Crohn's disease is higher in urban areas than in rural ones. Upper socioeconomic classes have a higher prevalence that is likely influenced by increased access to health services, but also by genetic and environmental factors [24].

In Europe, the overall incidence of Crohn's disease is of approximately 5.6 per 100,000 inhabitants [25], stabilizing or slightly increasing in recent years; the lowest rate of new cases seems to be in South Africa (0.3-2.6 cases per 100,000 people) and Latin America (0-0.03 cases per 100,000 people) [24].

4. Celiac disease

It is the most common hereditary food intolerance; it is a systemic disease, immune-mediated, triggered by gluten in genetically susceptible individuals. It represents one of the causes of occult obscure gastrointestinal bleeding. Just a small part of the celiac disease cases are clinically recognized, an issue shown in serological screening studies (21% in a recent European study) [26].

The prevalence is 1.5 up to 2 times higher in women, in first degree relatives of the affected persons (10 up to 15%), in patients with type I diabetes (between 3 and 16%) or with other autoimmune diseases (Hashimoto's thyroiditis (5%), autoimmune liver disease, Sjogren's syndrome, IgA nephropathy), IgA deficiency (9%), Down's syndrome (5%), Turner's syndrome (3%) [27].

5. Meckel's diverticulum

It is a relevant etiology in young patients (<25 years). Despite of the low frequency, it is the most common congenital anomaly of the gastrointestinal tract (about 2% of the general population). For patients with symptomatic diverticula, the male/female ratio is 3/1, and for the asymptomatic it is 1/1 [28].

Meckel's diverticulum occurs due to the incomplete obliteration of the yolk sac during the intestine embryogenesis. It has all the layers of the intestinal wall, and in 12% -21% of cases it may contain ectopic tissue (mucous membrane of the stomach, duodenum or even pancreatic ducts) [29].

Bleeding may be chronic and insidious or acute and massive. Diverticula of over 2 cm in size is the main risk factor that makes anatomic bleeding more likely [30].

6. NSAID enteropathy

The presence of ulcers in the small intestine should be considered in any patient with obscure gastrointestinal bleeding. Although most studies report angiodysplasia as the most common cause of obscure bleeding, a study in India, which involved 385 patients with OGIB, reported ulcers or erosions of the small bowel in 156 patients (the most common cause of OGIB) [31].

The prevalence of small intestine ulcers increases with age, with a rate of 13.04% reported in patients over 65 years old compared to 7.27% in patients under 40 [32]. The harmful effects of NSAIDs in the stomach and duodenum are well-established, but their involvement in the pathology of the small intestine is less certified.

At necropsy, nonspecific ulcers were detected at jejunum in 8.4% of patients who had a history of recent use of NSAIDs, compared to 0.6% in those who had not taken NSAIDs [33]. Other studies have enteroscopically objectified small intestine ulcers in 47% of patients treated with NSAIDs for rheumatoid arthritis [34].

7. Dieulafoy's lesion

It is a vascular malformation characterized by the presence of a large diameter vessel in the submucosa, which erodes the superimposed mucosa without associating an ulcer. Often, the lesion is located in the upper gastrointestinal tract, expressing itself as upper gastrointestinal bleeding.

8. Lesions due to portal hypertension can be causes of obscure bleeding

In patients with OGIB that have liver disease or portal hypertension (blood disorder, coagulopathy - thrombosis in the portal venous system), the existence of varices should be taken into account (collateral large veins, portosystemic) either in the small intestine, or in other unusual locations.

9. Radiation enteritis

Approximately 50% of patients with prostate, testicular, bladder, rectal, cervical and endometrial cancer require radiotherapy. Almost all patients undergoing abdominal or pelvic radiotherapy have acute lesions of the digestive mucosa, but only 5-15% of them develop radiation enteritis. Up to 50% of the patients with chronic radiation enteritis need surgery [36].

Obscure upper gastrointestinal bleeding-etiology

Obscure gastrointestinal bleeding is rarely expressed as upper gastrointestinal bleeding.

1. Cameron lesions

Cameron lesions were described for the first time by Cameron and Higgins in 1986 and are linear erosions or ulcerations of the stomach lining, localized at the diaphragmatic impressions hernial neck in patients with large hiatal hernia. They are noted in 5.2% of patients with hiatal hernias, the prevalence seems to be dependent on the size of the hernial sac and in two thirds of cases the lesions are multiple. From the clinical point of view, they are expressed as chronic gastrointestinal hemorrhage and iron deficiency anemia. Of these patients, about one third presented lesion recurrence and 17% developed complications (upper gastrointestinal hemorrhage-6.3% or persistent and recurrent iron deficiency anemia-8.3%) [37].

2. Angiodysplasia

Angiodysplasia is responsible for about 1.2 to 8% of the bleeding located in the upper digestive tract and it represents 5-10% of the causes of OGIB. They are located mainly in the duodenum. The presence of angiodysplasia in the upper gastrointestinal segments proved to be a predictor factor in the occurrence of these injuries at jejunal level [38].

3. Varices

Varices as a manifestation of portal hypertension can have any location in the gastrointestinal tract, but most commonly they are found in the distal segment of the esophagus.

Approximately 50% of patients with cirrhosis or portal hypertension present esophageal varices, and 5-33% gastric varices; their presence correlates with the severity of the liver disease and with the etiology of portal hypertension [63]. Sometimes gastric and esophageal varices are not identified as a cause of acute bleeding, being collapsed after a recent episode of upper gastrointestinal bleeding, or they can bleed in a chronic, occult manner, representing 1-5% of the cases of OGIB.

4. Dieulafoy's lesion

Dieulafoy's lesion is frequently located in the proximal stomach, the small flexure, subcardial; but there were reported cases in the duodenum, jejunum, ileum and colon.

Etiology is unclear, but it was noted that it occurs mostly in male patients with comorbidities (cardiovascular disease, chronic kidney disease, diabetes or alcohol abuse). This lesion can be easily overlooked during an endoscopic examination, given that the aberrant vessel cannot be seen unless it has active bleeding [35].

5. Gastric vascular ectasia

Gastric vascular ectasia is characterized by red spots aggregation that, when in a linear disposal in the antrum, is called "watermelon stomach" or gastric antral vascular ectasia (GAVE). Most often they are seen in women over 40, who have associated achlorhydria, atrophic gastritis or cirrhosis. Although initially it was considered that portal hypertension is involved in the etiology of gastric vascular ectasia, the pathogenesis remains unknown [40].

6. Portal hypertensive gastropathy

Portal hypertensive gastropathy occurs in up to 65% of patients with portal hypertension, approximately 65-90% of the patients have a mild form. In recent years, after frequently using ligature / sclerotherapy for esophageal varices, the incidence of portal hypertensive gastropathy has increased [41].

Obscure lower gastrointestinal bleeding-etiology

A small percentage of obscure gastrointestinal bleeding is manifested as lower bleeding.

1. Colonic angiodysplasia

It is the second cause, after diverticulosis, of lower GI hemorrhage in patients over 60 years. It may be responsible for about 6% of cases of lower gastrointestinal bleeding.

The prevalence of angiodysplasia in healthy patients aged 50, with colonoscopic assessment (screening) is 0.8%. The angiodysplastic lesions located at the colon are usually solitary and of large dimension. Ethnic variations are described: the colonic angiodysplasia in Japanese patients is located especially in the left colon, while in Western population - in the right colon, and the percentage of lesions with a dimension bigger than 5 mm detected in Japanese patients was significantly higher than in the patients in the West [42].

2. Colonic tumors

Worldwide, colorectal cancer is the second most common cancer in women (9.2% of all cancers) and the third most common in men (10.0% of total). The incidence of colorectal cancer is relatively equal in women and men. Age is a proven risk factor for colorectal cancer, the average age at diagnosis is 68 years [43]. Colorectal cancer occurs by the malignant transformation of adenomatous polyps into a series of steps that begin with different degrees of dysplasia.

In general, tumoral formations are highlighted endoscopically, but they may become causes of OGIB when visualisation is compromised by the presence of blood in the lumen, poor preparation for colonoscopy or incapacity to view the ampulla.

Other sources of obscure gastrointestinal bleeding

In addition to the intraluminal etiology, extraluminal sources, including aortoenteric fistulas, hemobilia and hemobilia pancreaticus may also present as OGIB and they represent about 1% of all OGIB [44].

Failure to maintain a high index of suspicion for these causes can lead to a significant delay in their diagnosis, such as unnecessary interventions performed for accidentally detected lesions at endoscopy.

The causes of bleeding at the small intestine vary with the patient's age. In patients under 40 years, the most frequent causes of obscure digestive hemorrhage in the small intestine are the inflammatory bowel disease and tumor. In patients over 40, the most frequent cause is angiectasia (the dilatation of blood vessels with small caliber - capillaries, venules, arterioles - or the lymphatic system), present in 30 up to 60% of the cases [45].

The epidemiology of gastrointestinal bleeding in elderly patients

The sources of bleeding are both the ones common to all age groups, and those associated especially with aging. Morbidity and mortality of gastrointestinal bleeding in patients over 60 years old are conditioned both by the nature of the lesion and the presence of associated diseases. The use of aspirin and other antiplatelet medications and anticoagulants increases the incidence of gastrointestinal bleeding in the elderly [46].

1. Upper gastrointestinal bleeding in the elderly

Beginning with the 1990s there has been a decreasing tendency in incidence of non variceal upper gastrointestinal bleeding, but recent analyses suggest that patients over 60 represent an increasing proportion of those who suffer from acute upper gastrointestinal bleeding. More than 70% of the flares of upper gastrointestinal bleeding occur in persons over 60, so advanced age was constantly identified as a risk factor for mortality among the patients that have upper gastrointestinal bleeding (perhaps because of the high prevalence of cardiovascular, pulmonary diseases and cancers compared to younger patients) [47].

2. Lower gastrointestinal bleeding in the elderly

The average age of the persons with acute lower GI bleeding ranges between 63-77 years. This trend is determined by the growth with the age of the incidence of diverticular bleeding, which represents the most common cause of lower GI bleeding in the elderly.

3. Obscure gastrointestinal bleeding in the elderly

About 20% of older people with GI hemorrhage do not have an identified cause of bleeding in the first standard upper/lower endoscopic exploration, and two thirds of these patients have a lesion localized in the small intestine [48].

Given the wide range of forms of manifestation of obscure bleeding, potential etiology and differences in their approach, precise clinical diagnosis is essential and it guides investigations and subsequent interventions. In recent years, advanced diagnosis technologies have been developed, such as capsule endoscopy, double-balloon enteroscopy and enterography CT, which has led to a better understanding of the etiologic profile of obscure gastrointestinal bleeding, allowing the establishment of specific and effective therapies.

The obscure GI hemorrhage is and will remain responsible for a high rate of mortality and morbidity, despite of all the progress made in the diagnosis and endoscopic/imaging and drug treatment.

Patients with obscure gastrointestinal bleeding have the risk of anemia-related complications (cardiovascular, neurological) or of multiple investigations (renal impairment because of contrast dye, organ perforation, infections). The patients' quality of life is affected and the overall costs are significant.

CONCLUSION

Obscure gastrointestinal bleeding is a pathology involving economic difficulties and of technical performance, discipline and medical ethics, reason why the challenge to refine old techniques and promote new ones in order to optimize the diagnosis and treatment remains valid.

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All the authors have the same contribution.

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