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Current view

Diminutive polyps and rectal bleeding: An overview

I. Bouzakis

SUMMARY

Rectal bleeding is very common in the general population. It is usually minimal, with outlet-type characteristics, but it can also be an expression of lower gastrointestinal bleeding. Colon investigation is usually indicated during rectal bleeding evaluation. Diminutive polyps cause no symptoms and they are an incidental finding in up to 50% of colonoscopies for various indications. Distal hyperplastic polyps are considered harmless. The natural history of adenomas, especially the diminutive ones, is largely unknown. Diminutive adenomas are rarely histologically advanced. Distal advanced diminutive adenomas or =3 distal diminutive tubular adenomas, can be markers of advanced proximal neoplasia. The importance of 1-2 diminutive tubular adenomas is highly controversial. Endoscopic removal of all polyps, although not specifically studied for diminutive ones, results in significant decrease of colorectal cancer incidence.

Key words: rectal bleeding, minimal rectal bleeding, adenomas, hyperplastic polyps, diminutive polyps, colorectal cancer, colonoscopy

INTRODUCTION

Rectal bleeding is a common symptom in the general population. Clinical presentation ranges from minimal bleeding with outlet type characteristics to massive bleeding with shock. Epidemiology, differential diagnosis and approach to the patient differ between minimal and lower gastrointestinal bleeding and will be examined, in brief, separately. It should be noted that while abundant literature emphasizes management options in patients with upper gastrointestinal bleeding, the literature that guides management of rectal bleeding is more limited, resulting in a controversial and not yet standardized approach.

Author for correspondence:
Ilias Bouzakis, 8-10 Kornarou str., 731 34 Chania, Greece,
Tel.: +28210 58498, Fax: +28210 58460,
e-mail: bouzakhl@cha.forthnet.gr

Minimal rectal bleeding

Although there is no standardized definition, in this review we use the term minimal or outlet-type bleeding to indicate the presence of small amounts of red blood on toilet paper or a few drops of red blood in the toilet bowl after defecation. Small amounts of red blood on the surface, but not intermixed with stool, is also considered outlet-type bleeding.

Epidemiology: By self-report, minimal rectal bleeding occurs in approximately 15% of the general population[1,2] being even more common in younger adults.[1,3] Of those with any rectal bleeding, only 14% had reported bowel problems in the previous year.[2]

Differential diagnosis: The most common causes are listed in Table 1. Hemorrhoids usually cause painless bleeding and are present in 27%-95% of cases,[4,5] while anal fissures usually cause a tearing pain with the passage of stool. Proctitis is often associated with mild diarrhea, tenesmus or passage of mucus. Neoplasms, especially polyps, are generally asymptomatic. Symptomat-

Table 1. Common causes of minimal rectal bleeding

Hemorrhoids
Anal fissures
Proctitis: infectious
IBD
radiation
Neoplasms: benign
malignant
Rectal ulcers

ic colorectal cancer (CRC) is usually left-sided, causing also abdominal pain and/or change of bowel habits.

Approach to the patient: A careful history must be followed by a detailed physical and rectal examination. Most authorities suggest also office-based anoscopy, since it is simple, with a high yield during a bleeding episode, and higher sensitivity than flexible video endoscopy for the detection of hemorrhoids.[6] Biochemical tests contribute little to the diagnosis and are more useful to discover any anemia or iron deficiency. Barium enema has no role in the initial evaluation since it does not examine distal rectosigmoid adequately, and cannot identify acutely bleeding lesions.[7] There is controversy regarding sigmoidoscopy or colonoscopy as the initial test of choice.[8-12]

Although there are no strict guidelines regarding the approach to patients with minimal rectal bleeding, we may suggest the following:

- Patients with constitutional symptoms, anemia, change of bowel habits, personal history of adenomas, CRC, or long-standing IBD, and family history of familial polyposis or CRC should be better evaluated with colonoscopy, regardless of their age.
- Patients aged 50 years or older: most medical societies suggest colon cancer screening in persons aged over 50 years,[13,14] therefore colonoscopy is recommended.
- Patients aged less than 50 years: if an actively bleeding lesion, such as hemorrhoids or anal fissure, is found on physical examination or anoscopy, then there is no need for further investigation. If no potential source is identified or bleeding is persistent, then, at least, sigmoidoscopy should be performed.

Lower gastrointestinal bleeding (LGIB)

In this review we use the term LGIB to indicate bleeding beyond the ligament of Treitz that is not minimal and has no outlet-type characteristics.

Epidemiology: LGIB is approximately one-fifth as common as upper GI bleeding and accounts, in the United States, for approximately 20-30 hospitalizations per 100,000 adults per year,[15,16] the rate increasing dramatically with age. Men are affected more frequently than women,[16] and in at least 70% of patients there is also a significant comorbid illness.[17,18] Most acute LGIB are self-limited, resulting in mortality of less than 5%.[15,16]

Differential diagnosis: The most common causes of LGIB are listed in Table 2. Of importance are the following:

- In up to 25% of patients, the source cannot be definitively identified.[16,17]
- Colonic diverticuli and vascular ectasias are the most usual causes,[15,19] typically causing painless bleeding. Usually they are not actively bleeding at the time of endoscopy,[19-21] making ascertainment of their role in bleeding difficult.
- Hemorrhoids account for 5%-10% of acute LGIB.[17] They are very common in the general population, therefore LGIB should not be ascribed solely to hemorrhoids until other lesions have been excluded.[19]

More detailed discussion about the causes of LGIB is beyond the purposes of this review.

Approach to the patient: LGIB encompasses a wide clinical spectrum ranging from trivial bleeding to massive hemorrhage with shock. In general, the approach to the patient is controversial and management depends in part on the specific diagnosis.[19] Regarding management options the most important points are the following:

- Evaluation of hemodynamic status and resuscitation are the cornerstones in the initial approach, concomitantly with history and examination.[22-23]
- In cases of aggressive bleeding most experts suggest nasogastric aspiration or esophagogastroduodenoscopy to exclude an upper GI source.[19,22,24]
- There is little if any role for barium enema and likely computed tomographic colonography.[19]
- Technetium-labeled RBC scintigraphy has doubtful accuracy, lacks therapeutic capability and its use is highly controversial.[25,26]

Table 2. Common causes of lower gastrointestinal bleeding

Diverticula
Vascular ectasias
Anal lesions: hemorrhoids
fissures
Inflammatory: IBD
ischemic colitis
radiation colitis
infectious colitis
Neoplasms
Postpolypectomy
Upper GI source
Small bowel source

- Angiography is able to detect active bleeding only down to a rate of 0.5-1.0mL/min and has therapeutic capabilities.[19,22] Current super-selective techniques appear to be more effective and safer than older ones.[27] Angiography is technically demanding and not widely available, resulting in limited use in poor surgical candidates.[19]
- Colonoscopy is considered the diagnostic procedure of choice,[28] shortening the hospital length of stay,[17,18] with therapeutic potential in 10%-15% of cases.[22,29] Whether it should be performed urgently (i.e. within 8-24 hours of presentation), with or without a purge preparation, or can be performed expectantly is an open question at this time.[19,22,29-31]
- Surgery is usually employed in 2 settings: massive or recurrent bleeding. Preoperative localization of the bleeding lesion with angiography or endoscopic tattooing helps to minimize its morbidity and mortality,[19, 32-34] avoiding blind colectomies.

COLONIC POLYPS

The term "colonic polyp" refers to a discrete mass or tissue that protrudes into the lumen of the bowel. They are usually classified as neoplastic, nonneoplastic and submucosal[35] (Table 3). The most interesting, points for this review, regarding colonic polyps, will be discussed briefly.

Adenomatous polyps (AP)

AP account for two-thirds of all colonic polyps and are thought to arise from a failure of the normal process of cell proliferation and cell death.[35] It seems that they evolve from a monoclonal expansion of an abnormal cell, although recent studies indicate that it may be polyclonal.[36]

Table 3. Classification of colonic polyps

Neoplastic: Adenomas: tubular
tubulovillous
villous
Carcinomas
Nonneoplastic: Hyperplastic
Mucosal
Inflammatory
Hamartomas: juvenile
Peutz-Jeghers
Submucosal: Lymphoid
Lipomas
Carcinoids
Metastatic
Colitis cystica profounda
Others

Classification: According to glandular architecture they are classified as tubular (>75% composed of a complex branching pattern), villous (>75% composed of elongated straight crypts) or tubulovillous (25%-75% villous component).[35] Tubular account for about 80% of all adenomas while tubulovillous and villous account for 5%-15% each.[36,37]

According to size AP are classified as <1cm and >1cm, the majority (60%-75%) being less than 1cm.[37,38] They tend to be larger when they are villous, in older and high-risk for CRC subjects, in symptomatic patients, and in countries where the prevalence of CRC is high.[37-40]

Dysplasia: All adenomas are dysplastic by definition.[35] The more recent classification scheme recognizes two grades of dysplasia: low (previous mild or moderate) and high (previous severe or carcinoma in situ or intramucosal carcinoma).[41] When dysplastic cells invade through muscularis mucosae into submucoca, then invasive carcinoma is present. The malignant potential of an adenoma is in direct proportion to its size, villous component, and severity of dysplasia.[38,42,43]

The term advanced adenoma refers to adenomas that are >1cm or have villous elements or for high grade dysplasia.[44] This definition covers all adenomas except tubular adenomas <1cm in size. Their natural history is largely unknown, but they seem to have a relative risk of about 3.5 for malignant transformation[38,42] compared to nonadvanced adenomas.

Flat and depressed adenomas: Up to 27%-36% of adenomas are flat (their height being less than one half their diameter) and up to 1% are depressed.[45-47] They are difficult to detect contributing to false negative colonoscopies. These lesions, originally thought to exist primarily in Japan, have now been described throughout the world.[46-50] Their natural history is largely unknown.[51] Flat adenomas seem to have the same malignant potential as equal-size polypoid lesions.[52] Depressed lesions arise without adenoma-carcinoma sequence,[53] resulting in advanced histology. In a meta-analysis,[52] their risk for containing invasive cancer was 8%, 43%, and 70%, for lesions <5mm, 6-10mm, and 11-15mm respectively. Their significance in U.S. and Europe is uncertain.[54]

Epidemiology: Prevalence is affected by 4 major factors: inherited risk for CRC in the population, age, gen-

der, and family history of CRC. In intermediate and high risk for CRC populations, adenomas are found in 30%-40% of individuals, where in low risk populations they are found in 12%.[35] Men have a 1.5 relative risk for adenomas compared to women.[39,55] In asymptomatic people at age 50 the prevalence of adenomas is about 25%-30%,[55-57] where as in those at age 70 it can be as high as 50%.[40] Five per cent of adenomas arise in individuals belonging to hereditary polyposis and nonpolyposis colon cancer syndromes.[35] First degree relatives of patients with adenomas or CRC have a relative risk of 2-3 for adenomas or CRC,[58] particularly when the affected person is younger than 60 years.[59]

Anatomic distribution: AP are uniformly distributed throughout the colon. [60,61] At age over 60 years, distribution demonstrates a shift to more proximal colonic locations.[39,55,62]

Management: Although the benefit of removing small polyps was not specifically addressed, the National Polyp Study in the U.S., found that endoscopic removal of all adenomas resulted in a 76%-90% decrease in CRC incidence compared to historic reference groups.[63] Therefore, the major gastroenterology societies recommend a complete clearing colonoscopy at the time of initial polypectomy to detect and resect all synchronous polyps.[64-66] The guidelines from these societies, for post-polypectomy surveillance, differ somewhat and may be summarized as following:

- A follow-up colonoscopy should be performed within a few months in patients with a large sessile polyp, when initial colonoscopy is incomplete, or in patients with numerous adenomas.
- Colonoscopy may be repeated in one year in patients with very high risk adenomas.
- Colonoscopy should generally be repeated in 3 years in patients with more than 3 adenomas or in those with one advanced adenoma.
- In patients with 1-2 small tubular adenomas, a 5-year surveillance interval is recommended.
- After one or two negative follow-up colonoscopies, subsequent surveillance may be performed every 5 years.
- Patients with FAP and other polyposis syndromes, and those with hereditary nonpolyposis colorectal cancer require a more stringent diagnostic approach and follow-up criteria and are not covered by these guidelines.

Hyperplastic polyps (HP)

They are sessile lesions grossly indistinguishable from adenomatous polyps, and have a characteristic stellate histologic appearance.[35] HP are typically located in the left colon and are less than 5mm in size,[67,68] although larger HP have been reported.[69]

Pathogenesis: Evidence is accumulating that HP arise through genetic alterations that lead to inhibition of apoptosis, especially the type that is triggered by loss of attachment of the surface epithelium to the basement membrane (anoikis).[70] HP may be pathogenetically related to adenomas since they appear in the same colon.[35] Additionally, a germline mutation of the APC gene caused a large number of HP to occurr in association with adenomas.[35]

Prevalence: It is not known with precision. Autopsy data report prevalence rates of 20%-35%, and observe a distal predominance,[40,71] while sigmoidoscopic screening of asymptomatic relatives of adenoma-prone kindreds revealed 26% with HP.[72] It also seems that prevalence increases with age.[62,73]

Serrated adenomas: 13% of HP display features of both hyperplastic and adenomatous transformation, termed serrated adenomas.[35] They tend to be larger than traditional HP, with proximal colon predilection and nuclear atypia. [74] There is considerable interobserver variation between pathologists at the distinction between serrated adenomas and HP.[70] A serrated pathway to colorectal neoplasia has been described resulting in microsatellite and chromosomal instability cancers.[70, 75-77] In one report, 37% of serrated adenomas contained areas of significant dysplasia and 11% had foci of intramucosal carcinoma.[78]

Management: Features of HP that seem to be markers of increased malignant potential include proximal location (especially cecum and ascending colon), multiplicity, size >10mm, and histologic features of serrated adenoma or mixed polyp (i.e. partly hyperplastic partly adenomatous).[70] These HP should be managed like adenomas.[76,79]

At the present time there is no a clear consensus regarding the management of patients with a single HP found at sigmoidoscopy. The bulk of evidence suggests that these endoscopies should be considered normal.[64,68,80] However, some studies suggest that distal HP are harbingers of proximal neoplasia.[62, 81-83]

Other nonneoplastic polyps

Mucosal polyps: They are small (<5mm) polyps com-

posed of normal mucosa.[35] They constitute 8%-20% of the material recovered by colonoscopic biopsies and have no clinical significance.[35]

Inflammatory pseudopolyps: They are irregularly shaped islands of residual intact colonic mucosa resulting from ulceration and regeneration that occurs in any severe colonic inflammation (IBD or infectious). They have no malignant potential.[35]

Juvenile polyps (JP): They consist of lamina propria and dilated cystic glands.[35] They are rare in adults and usually are solitary, rectal, pedunculated, and 3-20mm in diameter. Single JP should be removed because they often bleed, but they have no malignant potential.[84] Familial juvenile polyposis is a rare autosomal dominant syndrome resulting in multiple JP, and it is associated with an increased risk for CRC.[85]

Peutz-Jeghers polyps: They are hamartomas containing smooth muscle that extends into the lamina propria, with normal overlying epithelium.[35] They are almost always multiple, as part of the Peutz-Jeghers syndrome, where there is increased risk for gastrointestinal and non-gastrointestinal malignancy.[86,87]

DIMINUTIVE POLYPS (DP)

DP are defined as the polyps that measure 5mm or less in diameter.[35] They are very common, found in 20%-40% of screening colonoscopies.[62,83] An earlier concept that these lesions were almost always nonneoplastic, and therefore without clinical significance, has recently changed.

Pathology: DP of the right colon are more likely to be neoplastic,[67,88] while at the distal colon they could equally be adenomas or hyperplastic.[54] Most studies suggest that DP have a risk of less than 0.5% for high-grade dysplasia (HGD)[67,89] and they almost never contain invasive cancer.[90] An exception is patients with hereditary nonpolyposis colorectal cancer, where accelerated tumor promotion leads to advanced pathology of adenomas, even at small sizes.[73]

Natural history: Endoscopic polypectomy interrupts the natural history of polyps resulting in limited knowledge about their growth rate. In one study, cumulative risk of cancer at polyp site was only 2.5% at 5 years, 8% at 10 years, and 24% at 20 years.[91] Calculations based on age distribution studies estimated that adenomas with low grade dysplasia need 8 years to progress to cancer, where as those with HGD need 3-4 years.[35]

Data regarding DP are more limited. It seems that the majority of DP exhibit minimal growth rate averaging 0.5mm/year, and earlier reports of spontaneous regression have been recently refuted.[92] A study of untreated DP showed that after 2 years of follow-up, none grew to more than 0.5cm or developed HGD or cancer.[93] Available data also suggest that fewer than 5% of diminutive adenomas grow into advanced adenomas,[94] but there are no real data regarding the risk of advanced diminutive adenomas to become CRC.[95]

Clinical presentation and laboratory findings: DP typically cause no symptoms.[35] They are almost always an incidental finding, found in 20%-40% of screening colonoscopies,[62,83] and in more than 50% of colonoscopies for various indications.[67] People with known DP do not lose more than the normal amount of blood,[96] rendering FOBT an insensitive screening method for the detection of DP.[97]

Colonic investigation techniques and DP: Based on our knowledge of molecular genetic alterations in colon carcinogenesis, noninvasive methods for detecting altered human DNA in stool are now commercially available. In a recent study[98] it was found that their sensitivity for CRC was 52%, and for advanced adenomas was 13%. Their high cost combined with the limited effectiveness, has reduced their use in clinical practice.[99]

Double contrast barium enema (DCBE) has a sensitivity of about 50% for polyps >5mm[13,100] and about 30% for DP.[101,102] DCBE may perform less well in the rectosigmoid than in the rest of the colon.[7]

CT colonography (CTC) has emerged from the developmental phase, but its exact role is still uncertain. In a recent meta-analysis of 33 prospective studies,[103] the sensitivity of CTC for polyps <6mm, 6-9mm, and >9mm was 48%, 70%, and 85% respectively. Currently it is useful when conventional colonoscopy is incomplete, especially difficult, or risky. By 2010, the development of prepless CTC, and new software and hardware technology that improves polyp detection, could make CTC the primary CRC screening method.[95] Its cost-effectiveness is largely depended on the rate of references for conventional colonoscopy. If every patient found to have polyps is referred for polypectomy, then CTC will be far from being cost-effective.[44] Therefore, if 1-2 DP are the only finding, the current suggestion is to be ignored.[44]

Recently has begun, the clinical use of magnetic resonance colonography with reported sensitivity of 75% for polyps >5mm.[104] Similar to CT colonography, the cost-effectiveness of MR colonography will depend on the direct procedural costs, indirect costs associated with

incidental findings, and the rate at which subsequent conventional colonoscopy is required.[105]

Colonoscopy provides the most accurate evaluation of the colon.[54] It is the procedure of choice for screening asymptomatic high risk patients, and for surveillance of patients with prior adenomas or CRC,[13,54] but we should remember that it is not perfect. One report[106] found that the rare of missed adenomas <6mm, 6-9mm, and >9mm, was 27%, 13%, and 6% respectively. This observation suggests that some, if not most, "recurrent" adenomas are in fact missed lesions of the index colonoscopy. New endoscopic tools, such as high magnification chromoscopic endoscopy, spectroscopy, and optical coherence tomography promise to increase the yield of colonoscopy.[105]

Management: DP can be removed with cold biopsy forceps, hot biopsy forceps, simple fulguration, cold snare excision, or standard snare excision. Standard snare excision offers complete removal. Some authors advocate the use of cold forceps or cold snare excision for DP of ascending colon and cecum, because of the higher complication rate noted with hot biopsy in these areas.[67] Hot and cold biopsy removal is incomplete in 17% and 29% of cases respectively,[107,108] but the significance of this is unclear.

The prevalence of polyps in average risk asymptomatic persons is at least 20%-30%,[109] the majority been <10mm.[37,38] The overall survival of patients with excised DP is no worse than the general population,[110] therefore the most important issue regarding DP found on screening sigmoidoscopy or CT colonography is where they are markers of synchronous advanced adenomas or CRC.

There is some controversy about the significance of distal hyperplastic polyps. There are studies indicating that DP are markers of proximal neoplasia, irrespective of their histologic type.[111-113] Other studies have found that 21%-25% of patients with distal HP had proximal neoplasms, including 4-5% with advanced adenomas.[38,80,114,115] However, most resent studies,[13,62,83,116] including a meta-analysis,[117] concluded that patients with distal HP have no increased risk for proximal neoplasia compared with patients with no polyps, therefore colonoscopy is not necessary, nor do such patients need to be entered into a regular surveillance program.[64]

In patients with more than 3 or with advanced distal diminutive adenomas, most authors agree that full colonoscopy is warranted, since the risk for proximal advanced neoplasia or CRC is significantly increased.[13,44,62,83,118]

There is considerable debate about the management of patients with 1-2 tubular diminutive adenomas, with low grade dysplasia, found at sigmoidoscopy. Multiple studies indicate that these patients are not at increased risk for advanced proximal neoplasia,[42,110,119-124] while other studies have shown that the risk may be increased up to 3 fold,[62,80,83,111,112,119,125-127] probably being lower in persons aged under 60 years.[128] The considerable discrepancies between studies, are probably due to methodologic limitations, leaving this issue without conclusive answers.

Recent screening colonoscopy trials[56,62,83] reported that even patients with normal sigmoidoscopy, may have 3%-5% risk for proximal advanced neoplasms. Therefore, current guidelines[129-131] recommend that, patients with a diminutive adenoma found at sigmoidoscopy, should be offered a colonoscopy. On the other hand, an American Gastroenterological Association report on CT colonography[44], stated that polyps <6mm do not appear to be a compelling reason for colonoscopy and polypectomy. Both sides in the controversy agree that we need a natural history study of small polyps.[95]

Recommendations for relatives: There are data that relatives of patients with adenomas may have an increased risk for CRC, especially if the adenoma is advanced,[132] or the index relative is aged less than 50-60 years.[59,133] We should also keep in mind that the prevalence of adenomas in the general population is 30%-50%, therefore it is likely that most individuals have a first-degree relative with an adenoma. Probably, the most rational approach is, to suggest screening colonoscopy, if the index relative with adenoma is younger than 50 years old.[54]

DIMINUTIVE POLYPS AND RECTAL BLEEDING: AN OVERVIEW

Rectal bleeding is a very common symptom in the Western World, reported in more than 15% of the general population. Usually it is minimal, with outlet-type characteristics, but it can also be a manifestation of lower gastrointestinal bleeding.

In asymptomatic patients younger than 50 years old with minimal rectal bleeding, without risk factors for CRC, and an obvious source at clinical examination (i.e. bleeding hemorrhoids or fissures), no further investigation is necessary, but if bleeding recurs, then, at least, sigmoidoscopy is warranted. In all other cases of rectal bleeding, investigation of the entire colon is indicated.

Colonoscopy is considered the procedure of choice

for colon investigation, although it can have an up to 25% miss rate for small polyps. Double contrast barium enema is an accepted alternative, performing less well at the rectosigmoid. Computerized tomographic colononography is a promising new technique that is trying to find its place in diagnostic algorithms.

Diminutive polyps are symptomless and they are incidental findings in up to 50% of colonoscopies for various indications. Knowledge of their histology is mandatory. For most authorities, if distal hyperplastic polyps are the only finding, then colonoscopy should be considered normal. Diminutive adenomas are rarely histologically advanced, and less than 5% of them will ever progress into advanced adenomas. One advanced or =3 distal diminutive adenomas of any histology, are considered harbingers of proximal advanced neoplasia, therefore colonoscopy is indicated. The importance of 1-2 distal tubular diminutive adenomas is highly controversial. If they are found at sigmoidoscopy, although data are not firm, current guidelines also recommend colonoscopy. If they are the only finding at CT colonography, current guidelines suggest to ignore them.

Most studies, although not specifically addressed for diminutive polyps, have shown that, endoscopic removal of all adenomas, results in significant decrease of CRC incidence. Therefore, a complete clearing colonoscopy, during index polypectomy, is suggested.

Surveillance guidelines, regarding diminutive polyps, differ slightly between major gastroenterology societies. In general, patients with more than 3 or with advanced adenomas, should have surveillance colonoscopy at 3 years. In patients with 1-2 diminutive tubular adenomas, surveillance can safely extend to 5 years.

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