

## Anemia and Delayed Colon Cancer Diagnosis

August 10, 2019

Pathipati MP, Richter JM. Anemia and Delayed Colon Cancer Diagnosis. PSNet [internet]. 2019.

<https://psnet.ahrq.gov/web-mm/anemia-and-delayed-colon-cancer-diagnosis>

---

### Case Objectives

- Describe the initial evaluation for iron deficiency anemia in elderly adults.
- Understand that both upper endoscopy and colonoscopy are usually indicated in iron deficiency anemia.
- Recognize that patients with anemia on anticoagulation need a full evaluation for gastrointestinal bleeding.
- Define interval colorectal cancer.
- List common errors in management of iron deficiency anemia and colon cancer screening.

### The Case

An 81-year-old man with a history of atrial fibrillation on rivaroxaban presented to his primary care physician (PCP) with a hemoglobin of 11.1 g/dL (normal range in men: 13.5 to 17.5 g/dL). His hemoglobin had been normal 6 months earlier. A colonoscopy for colorectal cancer screening was normal 2 years prior to this presentation.

At this visit with his PCP, his vital signs were normal and physical examination was unremarkable. A fecal occult blood test was not performed. The patient was referred for an upper endoscopy, which showed mild gastritis. He was prescribed a proton-pump inhibitor and oral iron, and his dose of rivaroxaban was reduced. He was told that he would not need a repeat colonoscopy because his had not shown any lesions 2 years earlier. The patient had no family history of colon cancer.

Two months later, the patient's hemoglobin was found to be 8.5 g/dL. He was given two doses of intravenous iron and continued taking oral iron. His hemoglobin subsequently improved to 12 g/dL over the next 2 months.

Eight months later, the patient reported progressive fatigue and shortness of breath. A repeat hemoglobin was found to be 6.7 g/dL. A capsule endoscopy study and repeat upper endoscopy were performed and both were normal. He received a blood transfusion as well as additional iron infusions, resulting in an

improvement in his hemoglobin to 10 g/dL.

Four months later—2 years after his initial presentation—his hemoglobin fell again to 7.4 g/dL, and the patient received another blood and iron transfusion. Two days after this infusion, he presented to the emergency department with a bowel obstruction and was subsequently diagnosed with colon cancer. He underwent surgery to excise the mass and fortunately remains in remission.

## The Commentary

*Commentary by Mythili P. Pathipati, MD, and James M. Richter, MD*

This patient repeatedly presented with anemia, the cause of which was only discovered 2 years after his initial presentation. The first step in evaluating a new anemia in an older adult (after assessing for possible hypovolemia and optimizing circulatory function) is to attempt to discern the etiology—is it an iron deficiency anemia possibly due to inadequate intake, absorption, or blood loss, or is it something else? A standard evaluation may include a history and physical examination, complete blood cell count, reticulocyte count, renal function testing, iron studies, vitamin B12, folate, erythrocyte sedimentation rate, and C-reactive protein. If a patient is found to have iron deficiency anemia, which is the most common cause (and likely the case for this patient), then the diagnosis requires a search for the source of blood loss. In older patients, this search should generally focus on evaluation of the gastrointestinal (GI) tract, since it is likely to be the source of bleeding.<sup>(1,2)</sup>

Occult bleeding from the GI tract may be overlooked in the evaluation of anemia. In a study looking at 438 patients who presented with visit codes of rectal bleeding, hemorrhoids, or bloody stool at 10 adult primary care practices, clinicians failed to document a rectal exam in 29% of cases and failed to order imaging or a diagnostic procedure in 32% of cases.<sup>(3)</sup> Another study of 300 patients who presented to their PCP for rectal bleeding found that clinicians ordered a colonoscopy in 74% of patients for whom the procedure was indicated, and only 56% completed the colonoscopy within 1 year.<sup>(4)</sup>

In 20% to 40% of elderly patients with iron deficiency anemia, the source is the upper GI tract, and the etiologies are peptic ulcer disease, gastritis, esophagitis, or gastric cancer. In 15% to 30% of cases the blood loss is from the colon, most often caused by colon cancer, angiodysplasia, polyps, or colitis; 1% to 15% of patients have blood loss from other disorders. The source remains unknown in the other 10% to 40% of patients.<sup>(5)</sup> Given this distribution, both upper endoscopy and colonoscopy should be considered in the evaluation of a patient with iron deficiency anemia.<sup>(6)</sup> It is often unclear whether a finding on one endoscopic exam represents the true cause of occult bleeding, and thus both upper endoscopy and colonoscopy are recommended in most cases. In this case of an elderly patient presenting with iron deficiency anemia and no overt bleeding, the most likely source was chronic GI blood loss. Either a fecal occult blood test or a fecal immunochemical test could have been performed to confirm this—but regardless of the results, the patient warranted a repeat colonoscopy.

If endoscopy and colonoscopy do not reveal a source of the bleeding, the next step is evaluation of the small bowel. While less common than bleeding from the upper GI tract or the colon, small bowel bleeding can be a cause of iron deficiency anemia. Video capsule endoscopy is generally the test of choice to

evaluate suspected occult small bowel bleeding if endoscopy and colonoscopy with good visualization are negative. There are multiple other tests that can be used depending on the circumstances. If a proximal small bowel lesion is suspected based on clinical presentation, then push enteroscopy is the first test of choice. If video capsule is performed and is nondiagnostic, then computer tomographic enterography or magnetic resonance enterography should be performed. If no source is identified on these imaging modalities, then deep small bowel enteroscopy is performed, and if no source is identified on this, then computed tomographic angiography can be considered. The choice of test of course depends on the rate of bleeding, patient characteristics, and the degree of suspicion for a small bowel lesion.<sup>(7)</sup> The patient in this case underwent upper endoscopy first and capsule endoscopy second for small bowel evaluation, but—likely reassured by the negative colonoscopy 2 years earlier—there was no evaluation for a colonic source of bleeding. Mild gastritis was noted on his first endoscopy but would not account for the severity of his anemia. Capsule endoscopy rarely results in meaningful inspection of the colon, and it has not been validated or established as a means of screening for colon cancer.

Although this patient was on anticoagulation, he should have undergone further testing to evaluate for occult GI bleeding rather than just have the dose reduced. The data are conflicting regarding the effects of anticoagulation on fecal occult blood testing. One study showed that patients who were on aspirin, nonsteroidal anti-inflammatory drugs (NSAIDs), clopidogrel, or warfarin had a lower positive predictive value of fecal occult blood testing for advanced colorectal neoplasia compared with patients not taking these agents.<sup>(8)</sup> A different study showed that patients who used low-dose aspirin had markedly higher sensitivity for detecting advanced colorectal neoplasms compared to patients not using aspirin.<sup>(9)</sup> Another study comparing patients taking warfarin to those taking no antithrombotic found no difference in the detection rates of carcinomas between the warfarin group and the no-antithrombotic group.<sup>(10)</sup> In any case, iron deficiency anemia or a positive fecal occult blood test in a patient on anticoagulation should not be treated as a false positive and should be viewed as a real finding requiring evaluation. Thus, being on anticoagulation does not reduce the importance of searching for a site of bleeding. In fact, anticoagulation is more likely to unmask a bleeding source than to cause bleeding from a normal mucosa.<sup>(11)</sup>

Unfortunately, colon cancers can be missed or develop between screening colonoscopies; such cancers are referred to as interval colorectal carcinomas. The Colorectal Cancer Screening Committee of the World Endoscopy Organization has standardized the definition of an interval colorectal carcinomas as "colorectal cancer diagnosed after a screening or surveillance exam in which no cancer is detected, and before the date of the next recommended exam."<sup>(12)</sup> A small but significant number of interval cancers are identified after colonoscopy for colorectal cancer screening.<sup>(13)</sup> A population cohort study found that 6% of colorectal cancers develop within 6 to 60 months of a screening colonoscopy.<sup>(14)</sup> In a study looking at 75,314 patients who underwent colonoscopy for screening or diagnostic purposes, interval cancers were more common in patients age 60 or older, cancers that developed on the right side of the colon and in the hepatic flexure, and in patients who did not undergo a complete exam.<sup>(15)</sup>

While some interval colorectal carcinomas may not have been detectable at the time of the initial colonoscopy, others will likely be overlooked. Endoscopist experience in screening colonoscopy is an important factor, as less experienced providers are more likely to not complete the full exam or not identify lesions. Endoscopists performing screening colonoscopies should have lifetime colonoscopy experience of at least 400 procedures together with a minimum number of 200 annual screening colonoscopies to have

adequate completion rates.(16) Screening colonoscopies performed by nongastroenterologists are more often associated with the appearance of interval colorectal cancer, which may imply that some of these colorectal cancers were missed.(17) Other factors that can influence the development of interval colorectal cancers are the quality of preparation for the procedure, age of the patient, family history of gastrointestinal neoplasia, and missed or incompletely excised lesions.(17) For the patient in this case, the endoscopist who performed his previous colonoscopy may have missed a cancer or failed to recognize a polyp that would later become a cancer.

A question implicit in this case is when it is appropriate to perform screening or diagnostic colonoscopy after age 75. The US Preventive Services Task Force, the American College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy all recommend that adults age 50 to 75 should be screened for colorectal cancer, with subsequent intervals of every 10 years in the absence of any personal history of adenomas or family history of colorectal cancer. They also recommend that those between ages 76 to 85 should be screened on an individual basis considering the patient's preferences, overall health, life expectancy, and prior screening history.(18,19) While screening colonoscopies in elderly patients (older than 80) are generally not recommended given the shorter mean life expectancy, diagnostic colonoscopies are different. For patients with iron deficiency anemia or evidence of bleeding, generally either or both upper endoscopy and colonoscopy should be performed.(20) Patients with hemoglobin levels less than 10 g/dL (as was the case for this patient) should be investigated expeditiously with a colonoscopy first, and if negative, then endoscopy.(21)

In this case, errors in managing anemia led to a diagnostic delay. More specifically, there was an anchoring bias associated with the recently performed colonoscopy, which unduly shaped expectations for the patient's course. We believe this anchoring was associated with two subsequent errors in judgment. First, it led to a lapse in clinical reasoning regarding the value of the test. Colonoscopies are a useful screening tool (with an estimated sensitivity of 75% to 93% for adenomas 6 mm or larger) (22), yet they do not identify all cancers or development of interval cancers. Second, it led the clinician to search for an alternative explanation for the patient's blood loss, e.g., that anticoagulation could explain even severe anemia.

Having a normal colonoscopy is reassuring, but it does not guarantee that an interval cancer will not develop. From the clinician's point of view, it is important to ensure that prior screening tests do not overtly bias interval evaluation of new symptoms. Perhaps the most important step institutions and their clinicians can take to avoid this error is to establish and follow clear protocols for diagnostic testing. For instance, suspected GI bleeds should be worked up carefully regardless of the results of a previous colonoscopy. Based on the clinical presentation, even with a colonoscopy 2 years prior that did not identify any lesions, the patient should have undergone colonoscopy, which almost certainly would have found the cancer, prevented the bowel obstruction, and improved the patient's likelihood of cure.

## Take-Home Points

- The workup for iron deficiency anemia should include a systematic search for a source of blood loss, which could be found anywhere in the gastrointestinal tract.

- Both colonoscopy and upper endoscopy should be considered in patients with iron deficiency anemia, because it is often unclear whether a finding on one endoscopic exam represents the true cause of occult bleeding.
- Being on anticoagulation does not reduce the importance of evaluating a patient with iron deficiency anemia; anticoagulation is more likely to accelerate an existing bleed than to cause bleeding from normal mucosa.
- Colonoscopy is imperfect. Almost 6% of colorectal carcinomas are recognized within 6 to 60 months of an apparently normal screening colonoscopy.
- In high-risk patients, there should be a low threshold for repeating a colonoscopy.
- Although screening colonoscopies in patients older than 80 are generally not recommended, diagnostic colonoscopies for symptomatic patients should be performed regardless of prior screening colonoscopy results.

**Mythili P. Pathipati, MD** Resident Physician Massachusetts General Hospital Boston, MA

**James M. Richter, MD** Attending Physician Director, Gastroenterology Quality Management  
Massachusetts General Hospital Boston, MA

**Faculty Disclosure:** *Drs. Pathipati and Richter have declared that neither they, nor any immediate member of their families, have a financial arrangement or other relationship with the manufacturers of any commercial products discussed in this continuing medical education activity. In addition, the commentary does not include information regarding investigational or off-label use of pharmaceutical products or medical devices.*

**Acknowledgment:** This case was produced in cooperation with the [Primary-Care Research in Diagnosis Errors](#) (PRIDE) Learning Network.

## References

1. Rockey DC, Cello JP. Evaluation of the gastrointestinal tract in patients with iron-deficiency anemia. *N Engl J Med.* 1993;329:1691-1695. [\[go to PubMed\]](#)
2. Cook JD, Skikne BS. Iron deficiency: definition and diagnosis. *J Intern Med.* 1989;226:349-555. [\[go to PubMed\]](#)
3. Weingart SN, Stoffel EM, Chung DC, et al. Working up rectal bleeding in adult primary care practices. *J Eval Clin Pract.* 2017;23:279-287. [\[go to PubMed\]](#)
4. Percac-Lima S, Pace LE, Nguyen KH, et al. Diagnostic evaluation of patients presenting to primary care with rectal Bleeding. *J Gen Intern Med.* 2018;33:415-422. [\[go to PubMed\]](#)
5. Smith DL. Anemia in the elderly. *Am Fam Physician.* 2000;62:1565-1572. [\[go to PubMed\]](#)
6. Bull-Henry K, Al-Kawas FH. Evaluation of occult gastrointestinal bleeding. *Am Fam Physician.* 2013;87:430-436. [\[go to PubMed\]](#)

7. Gurudu SR, Bruining DH, Acosta RD, et al; ASGE Standards of Practice Committee. The role of endoscopy in the management of suspected small-bowel bleeding. *Gastrointest Endosc.* 2017;85:22-31. [\[go to PubMed\]](#)
8. Sawhney MS, McDougall H, Nelson DB, Bond JH. Fecal occult blood test in patients on low-dose aspirin, warfarin, clopidogrel, or non-steroidal anti-inflammatory drugs. *Dig Dis Sci.* 2010;55:1637-1642. [\[go to PubMed\]](#)
9. Brenner H, Tao S, Haug U. Low-dose aspirin use and performance of immunochemical fecal occult blood tests. *JAMA.* 2010;304:2513-2520. [\[go to PubMed\]](#)
10. Kershenbaum A, Lavi I, Rennert G, Almog R. Fecal occult blood test performance indicators in warfarin-treated patients. *Dis Colon Rectum.* 2010;53:224-229. [\[go to PubMed\]](#)
11. Lin OS, Kozarek RA, Schembre DB, et al. Screening colonoscopy in very elderly patients: prevalence of neoplasia and estimated impact on life expectancy. *JAMA.* 2006;295:2357-2365. [\[go to PubMed\]](#)
12. Sanduleanu S, Le Clercq CMC, Dekker E, et al; Expert Working Group on 'Right-sided lesions and interval cancers,' Colorectal Cancer Screening Committee, World Endoscopy Organization. Definition and taxonomy of interval colorectal cancers: a proposal for standardising nomenclature. *Gut.* 2015;64:1257-1267. [\[go to PubMed\]](#)
13. Ertem FU, Mehrotra A, Gourevitch RA, Ladabaum U, Schoen RE. 636 What is the expected incidence of interval colorectal cancer (CRC) for an endoscopist in active clinical practice? *Gastrointest Endosc.* 2017;85:AB93. [\[Available at\]](#)
14. Samadder NJ, Curtin K, Tuohy TMF, et al. Characteristics of missed or interval colorectal cancer and patient survival: a population-based study. *Gastroenterology.* 2014;146:950-960. [\[go to PubMed\]](#)
15. Richter JM, Campbell EJ, Chung DC. Interval colorectal cancer after colonoscopy. *Clin Colorectal Cancer.* 2015;14:46-51. [\[go to PubMed\]](#)
16. Jover R, Herráiz M, Alarcón O, et al; Spanish Society of Gastroenterology; Spanish Society of Gastrointestinal Endoscopy Working Group. Clinical practice guidelines: quality of colonoscopy in colorectal cancer screening. *Endoscopy.* 2012;44:444-451. [\[go to PubMed\]](#)
17. Singh H, Nugent Z, Mahmud SM, Demers AA, Bernstein CN. Predictors of colorectal cancer after negative colonoscopy: a population-based study. *Am J Gastroenterol.* 2010;105:663-673. [\[go to PubMed\]](#)
18. Bibbins-Domingo K, Grossman DC, Curry SJ, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA.* 2016;315:2564-2575. [\[go to PubMed\]](#)
19. Rex DK, Boland CR, Dornitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol.* 2017;112:1016-1030. [\[go to PubMed\]](#)
20. Chait MM. Lower gastrointestinal bleeding in the elderly. *World J Gastrointest Endosc.* 2010;2:147-154. [\[go to PubMed\]](#)

21. Smith DL. Anemia in the elderly. In: Garrison C, ed. Iron Disorders Institute Guide to Anemia. Cumberland House: 2009;9:96-103. ISBN: 9781581826920.

22. Lin JS, Piper MA, Perdue LA, et al. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. JAMA. 2016;315:2576-2594. [\[go to PubMed\]](#)

*This project was funded under contract number 75Q80119C00004 from the Agency for Healthcare Research and Quality (AHRQ), U.S. Department of Health and Human Services. The authors are solely responsible for this report's contents, findings, and conclusions, which do not necessarily represent the views of AHRQ. Readers should not interpret any statement in this report as an official position of AHRQ or of the U.S. Department of Health and Human Services. None of the authors has any affiliation or financial involvement that conflicts with the material presented in this report. [View AHRQ Disclaimers](#)*