Recurrent Obscure Gastrointestinal Bleeding

Peter J. Rizzolo, MD, and Warren P. Newton, MD

Routine diagnostic studies can locate the source of gastrointestinal bleeding in the vast majority of persons. In approximately 5 percent of persons, however, the source remains obscure despite sophisticated studies. Our inability to localize the source of bleeding in these individuals illustrates the limits of available diagnostic technology.

In an elderly patient who requires repeated diagnostic studies, attendant morbidity can be a limiting factor in the aggressive pursuit of the source of bleeding. In this paper, we discuss the usefulness of empiric hormonal therapy for the frail elderly patient who would be a poor surgical candidate or who could not tolerate repeated invasive procedures.

Obscure intestinal bleeding is known to remit spontaneously. In the individual patient, therefore, it is not possible to ascribe the cessation of bleeding to oral hormonal treatment. Because randomized, controlled studies have not addressed this question, clinicians caring for a frail older person bleeding from an obscure lesion should consider empiric hormonal therapy as a reasonable treatment option.

Case Report

Presentation

A 79-year-old man complained of a spell of weakness associated with 2 to 3 days of frequent dark brown stools. His hematocrit, which was measured at the nursing unit of his retirement community, was 38 percent. On further examination, he was without any constitutional, cardiovascular, or other digestive tract symptoms. His medical history was significant for two episodes of lower gastrointestinal bleeding 12 years earlier, at which time he underwent flexible sigmoidoscopy, barium enema, two upper endoscopies, and upper gastrointestinal and small bowel follow-through contrast studies, which were without definitive diagnosis. A total of 11 units of packed red cells were administered. The bleeding eventually stopped without specific therapy. Other medical problems included a history of hypertension, an old myocardial infarction, chronic atrial fibrillation, congestive heart failure, gout, and a stroke 1 year earlier that left no residual neurologic damage. His current medications included digoxin, furosemide, potassium chloride (extended release tablets), terazosin hydrochloride, aspirin, and allopurinol. The patient was a retired professor of statistics; he was married and living in a "life-care" community. He denied any family history of polyps, cancer, or coagulopathy.

On examination his blood pressure and heart rate were normal and without orthostatic changes. Other findings of the physical examination were remarkable in that the patient had good color, normal oral mucosa, no evidence of bruising or bleeding, a benign abdomen, and dark brown guaiac-positive stool. A complete blood count showed his hemoglobin was 12.9 g/dL, hematocrit 37 percent, with normal indices and platelets, normal coagulation studies, and a normal chemistry panel. The patient was given fluids overnight and scheduled for colonoscopy; aspirin was discontinued.

Endoscopy and colonoscopy were performed several days later. In the interval, the patient's hematocrit fell from 37 to 30 percent. Findings on an upper endoscopy were normal. Findings on colonoscopy showed two small, benign-appearing adenomatous polyps, not believed to be the source of bleeding. Melenic stool was noted at the terminal ileum, but an actively bleeding site was not seen. Because of continuing melena, intestinal radionuclide imaging, including a scan for Meckel's diverticulum, and enteroclysis were performed; again, no bleeding site was found. The patient was given four units of packed red cells and the melena decreased. After consultation with a surgeon and gastroenterologist, the patient and the managing physicians decided against an angiogram, and the patient was discharged to home.

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From the Department of Family Medicine, The School of Medicine, University of North Carolina at Chapel Hill. Address reprint requests to Peter J. Rizzolo, MD, Department of Family Medicine, The School of Medicine, CB #7595, William B. Aycock Building, University of North Carolina at Chapel Hill, Chapel Hill, NC 27599-7595.

Further Course

Three days later the patient's hematocrit had dropped to 25 percent, and he was readmitted for transfusion. An angiogram was done, the results of which showed no evidence of active bleeding. A laparotomy was considered but rejected in view of the operative risk and the lack of a localized lesion. The melena persisted for 2 more days, and the patient was given a total of 5 units of packed red cells.

Nine days after discharge, the patient had another episode of melena, his hematocrit dropped from 32 to 28 percent, and he experienced shortness of breath on exertion. Repeat endoscopic and colonoscopic examinations did not show any active source of bleeding. Repeat intestinal radionuclide imaging at the time of a second in-hospital episode of melena showed no active bleeding. Results of coagulation studies, including bleeding time and serum calcium, continued to be normal.

At this time the following strategies were discussed with the patient and his surgeon, gastroenterologist, and vascular radiology consultants: (1) watchful waiting, transfusions sufficient to raise the hematocrit to at least 30 percent, and hope that the bleeding would gradually stop as it had 12 years before; (2) further work-up of probable bleeding in the small bowel using either a pediatric colonoscope or an enteroscope, an experimental long flexible endoscope developed to view the small bowel; (3) a laparotomy with intraoperative endoscopy; (4) a provocation angiogram, in which urokinase would be infused before the angiogram; and (5) empirical treatment with hormonal therapy for control of bleeding. The patient opted for an upper endoscopy with a pediatric colonoscope, transfusion to support hematocrit levels, and treatment with hormones while the possibility of enteroscopy was investigated. The endoscopic examination with a pediatric colonoscope showed no source of bleeding; after the patient was given about 8 units of packed red cells, the melena again stopped, and he was discharged home on a regimen of norethindrone 1 mg and mestranol 0.05 mg (Ortho-Novum 1/50).

Three days later, the patient passed a dark brown stool positive for occult blood, and his hematocrit dropped from 34 to 27 percent. Again, coagulation studies were normal; an abdominal computed tomographic scan was normal. Enteroscopic examination proved to be impractical: our gastrointestinal consultants were unable to get an enteroscope, and travel to where one was available was not practical because of the patient's continued bleeding. After 8 more units of packed red cells were given, the melena stopped, and he was again discharged on birth control pills, with arrangements made for outpatient transfusions. The potassium chloride sustained-release tablet was changed to potassium chloride oral solution because of the possibility of small bowel ulceration with the long-acting form.

Outpatient transfusions were required weekly for 4 weeks, for a total of 9 units of packed red cells, but the melena gradually disappeared. Five weeks after starting birth control pills, the patient had a stable hematocrit and no evidence of gastrointestinal bleeding.

Eight weeks after starting birth control pills, the patient came to his primary physician complaining of a condition diagnosed as superficial thrombophlebitis. He was taken off birth control pills; the gastrointestinal bleeding did not recur.

Figure 1 was prepared by the patient on his own initiative and presented to the author as a record of the hematocrit changes and the units of blood given. It very nicely documents the change in the rate of drop in the hematocrit readings following the initiation of the birth control pills.

Discussion

The most likely sources of bleeding in patients with severe, recurrent occult gastrointestinal bleeding of the small bowel are angiodysplasia, telangiectasia, and arteriovenous malformations. While some pathologists debate the histologic features of these lesions, angiodysplasia consists of irregular shaped clusters of arterial, venous, and capillary vessels located in the submucosa of the gastrointestinal tract. Telangiectasia are fine, linear, irregularly shaped lesions created by dilatation of preexisting small vessels. In many of these lesions there is a small central arteriole with radiating branches also referred to as spider telangiectasia. Arteriovenous malformations consist of tangles of abnormal blood vessels of varying size, many of which have structures intermediate between arteries and veins.

Diagnosis

The diagnosis of obscure gastrointestinal bleeding remains difficult. Gastroduodenoscopy and

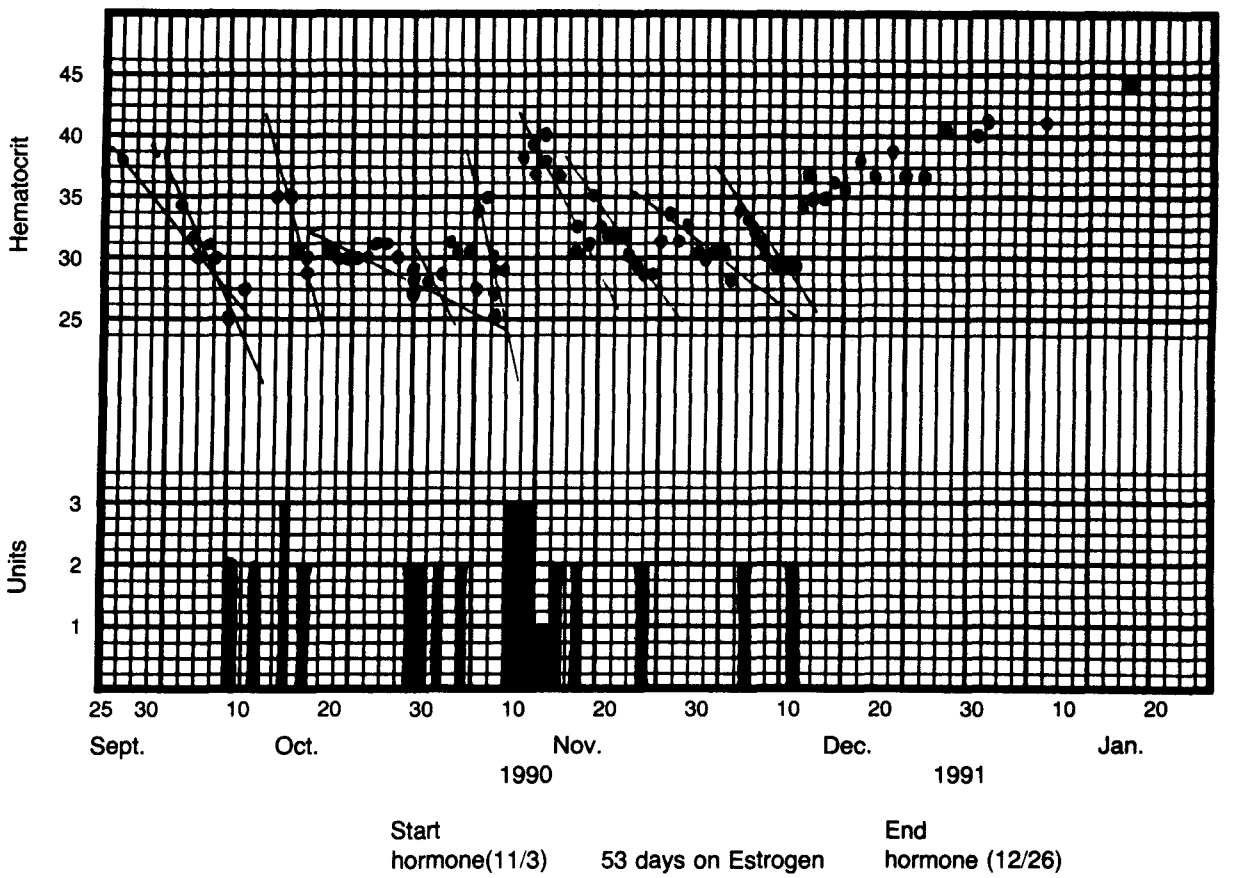

Figure 1. Patient-prepared graph of hematocrit level changes and units of blood given during course of illness.

colonoscopy are procedures that are available in most parts of the United States. Despite evidence that interobserver variability is substantial, the sensitivity of these studies in patients with gastrointestinal bleeding is reported in excess of 90 percent.[1]

In our patient, who had falling hematocrit levels and melenic heme-positive stools, two technetium scans failed to locate a bleeding site. In a recent report, Bentley and Richardson[2] presented data suggesting that red cell scanning is an unreliable diagnostic technique for localization of gastrointestinal bleeding, especially when the source is in the small bowel. They reviewed several previous small studies with cumulative results indicating a sensitivity of 82 percent. Their study, the largest reported series thus far, indicated only a 52 percent sensitivity. When the results were divided by the site of bleeding, the test was even less sensitive in localization of small bowel bleeding. The sensitivity of the tagged red cell scans in detecting small bowel bleeding was only 25 percent.

Angiographic localization of bleeding requires bleeding at the rate of 0.5 mL/min.[3] If the bleeding has stopped or is slower than the 0.5 mL/min, the angiography results will be negative. Because it is not possible to know with certainty the rate of bleeding or whether the patient is still bleeding, the individual could be subject to this invasive study unnecessarily. The angiogram done in our patient was not diagnostic and unfortunately resulted in a large inguinal hematoma at the site of injection of the angiographic material.

Several other, more invasive diagnostic procedures were considered for our patient. Enteroscopy, the visualization of the small bowel by a 150-cm long endoscope, has been reported to locate the lesion in two-thirds of a series of patients with obscure gastroenterologic bleeding. Unfortunately, its usefulness for locating small bowel lesions is limited by the limited control of the head of the instrument, and there is a lack of general availability of the device.

Another possible procedure was a provocation angiogram, using urokinase to prolong bleeding to improve the sensitivity of the angiogram. For this patient, who had a history of stroke, the

possible risks of this procedure were considered too great.

A final possibility was laparotomy with intraoperative endoscopy. Our surgical consultants estimated that we could expect only a 50 percent chance of locating the bleeding site with this procedure. In addition, Desa, et al.[4] reported that in 12 patients who had laparotomy with endoscopy, the bleeding site was found in only 3. They regarded the presence of fresh blood as indicating the site of bleeding, and on that basis they did either local or segmental resection. One-third of the patients who had bowel resection had recurrence of bleeding postoperatively. Two of the 12 patients died postoperatively. These results do not make intraoperative endoscopy a reasonable choice, especially in an elderly patient who has significant cardiovascular risk factors.

Hormonal Treatment of Obscure Gastrointestinal Bleeding

There is evidence that estrogens, or the combination of progesterone and estrogens, reduce bleeding in persons with gastrointestinal bleeding. Van Cutsem, et al.[5] described a double-blind placebo-controlled crossover trial in 10 patients with severe bleeding from gastrointestinal vascular malformations. They gave a daily dose of 0.05 mg of ethinylestradiol plus 1 mg of noresthisterone by mouth. Patients receiving the hormones had significantly decreased transfusion needs, which dropped from an average of 10.9 units to 1.1 units during the 12-month trial. In addition, case series or case reports have found success using estrogens or combination estrogen-progesterone therapy in persons with epistaxis secondary to hereditary telangiectasia[6-9] and gastrointestinal angiodysplasia.[10] The importance of adding progesterone, dosage, and duration of treatment remains unclear.

How estrogen-progesterone combination therapy would reduce bleeding from telangiectasia, arteriovenous malformation, or angiodysplasia is not known. Findings from electron microscopy suggest that estrogens can restore disrupted endothelium of abnormal blood vessels.[10] The delayed onset of effectiveness in our patient and in other patients is consistent with this theory of restoration of endothelial lining.

A direct effect of hormonal therapy on coagulation mechanism also is likely, but it has not been established.[11]

The thromboembolic risks associated with use of estrogens are well known.[12-15] Physician and patient must balance the risk of continued bleeding against the possibility of complications of transfusion and cardiovascular risks. Our patient experienced two side effects from hormonal therapy, gynecomastia and a superficial thrombophlebitis.

Physicians should consider using hormonal therapy in elderly patients with obscure gastrointestinal bleeding, in whom multiple studies fail to reveal the source of bleeding, or in very frail elderly, in whom invasive procedures, such as angiography, small bowel enteroscopy, or laparotomy, might not be acceptable options.

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