## Recurrent obscure gastrointestinal bleeding: Dilemmas and success with pharmacological therapies. Case series and review

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The present article describes three difficult cases of recurrent bleeding from obscure causes, followed by a review of the pitfalls and pharmacological management of obscure gastrointestinal bleeding. All three patients underwent multiple investigations. An intervening complicating diagnosis or antiplatelet drugs may have compounded long-term bleeding in two of the cases. A bleeding angiodysplasia was confirmed in one case but was aggravated by the need for anticoagulation. After multiple transfusions and several attempts at endoscopic management in some cases, long-acting octreotide was associated with decreased transfusion requirements and increased hemoglobin levels in all three cases, although other factors may have contributed in some. In the third case, however, the addition of low-dose thalidomide stopped bleeding for a period of at least 23 months.

**Key Words:** Obscure gastrointestinal bleed; Pharmacological therapy

### Case 1

A 76-year-old woman presented with melena and anemia in January 2001. The patient had a history of hypertension and peptic ulcer disease while on anti-inflammatory drugs, which were discontinued after diagnosis. Gastroscopy on initial hospitalization and a small bowel follow-through x-ray were normal. Colonoscopy revealed diffuse, small AE vessels in the colon that were more severe on the left side. Coagulation was not attempted at that time because no definite bleeding site was identified. Due to ongoing recurrent drops in hemoglobin levels and a perceived failure to identify a definite bleeding site, medical therapy was attempted.

### Case 2

The patient was a 74-year-old man who presented with severe constipation in February 2001. Colonoscopy revealed diffuse, small AE vessels in the colon that were more severe on the left side. Coagulation was not attempted at that time because no definite bleeding site was identified. Due to ongoing recurrent drops in hemoglobin levels and a perceived failure to identify a definite bleeding site, medical therapy was attempted.

### Case 3

The patient was a 77-year-old man who presented with melena and anemia in May 2001. Colonoscopy revealed diffuse, small AE vessels in the colon that were more severe on the left side. Coagulation was not attempted at that time because no definite bleeding site was identified. Due to ongoing recurrent drops in hemoglobin levels and a perceived failure to identify a definite bleeding site, medical therapy was attempted.
The patient was initially treated with combination estrogen and progesterone therapy, but developed deep venous thrombosis that required the discontinuation of hormones, and for warfarin to be prescribed from July to October 2001. Two other colonoscopies were unsuccessful in reaching beyond the distal transverse colon, with no bleeding AE vessels being identified. Because of continued bleeding, additional pharmaceutical therapy was planned. After one week of increasing subcutaneous doses of octreotide (from 50 μg/day to 100 μg twice daily [Sandostatin LAR; Novartis, Switzerland]), the long-acting release version of octreotide (Sandostatin LAR; Novartis, Switzerland) at 20 mg once every 28 days was started in November 2001 and continued on a trial basis until January 2002. While on octreotide, the patient’s transfusion requirements dropped considerably. Off octreotide (stopped at the request of the patient), transfusion requirements increased again. As a result, octreotide was restarted in April 2002. Again, transfusion requirements fell significantly (Figure 1). The patient did not receive any anticoagulants or antiplatelet medications during this time. Toward October 2002, she presented with a history of dysphagia lasting several weeks. A gastroscopy performed in late October 2002 revealed a mass in the lower esophagus. Pathology revealed adenocarcinoma. The patient died approximately five months after resection of the lesion.

CASE 2

An 82-year-old woman was referred for obscure gastrointestinal bleeding in October 2001. The patient’s history was significant for heart failure due to valvular disease, interstitial lung disease, hypothyroidism and type 2 diabetes mellitus. Her medications consisted of acetylsalicylic acid (ASA) started some time earlier, prostaglandin E2 (Cytotec [misoprostol]), ferrous sulfate, pantoprazole, nitroglycerin, furosemide, thyroxine, metformin and glyburide. She reported taking rofecoxib very rarely for occasional knee pain. Her anemia dated from 1998, and a myelodysplastic syndrome was suspected. After a bone marrow biopsy failed to support this suspicion, and because of occult gastrointestinal bleeding confirmed by positive fecal occult blood tests and declining hemoglobin levels, she was referred to gastroenterology. She underwent four normal gastroscopies and two colonoscopies that revealed sigmoid diverticulosis and a flat polyp (that was removed) at the ileocecal valve. A series of upper gastrointestinal endoscopies and a small bowel follow-through were normal. Because of mild renal failure and persistent anemia, she was started on intramuscular erythropoietin injections every week in early 2002; despite this, she continued to require transfusions.

Prostaglandin E2 cytoprotection was definitively stopped in late November 2002 and the patient was started on subcutaneous octreotide 100 μg twice daily in early December 2002, and switched to octreotide LAR 10 mg intramuscular/month two weeks later. Except for the initial difficulty in controlling blood glucose, she tolerated octreotide LAR until mid March 2003, when she experienced abdominal pain. Initial investigation with coiled computed tomography raised the possibility of a bowel infarction; however, pneumatosis intestinalis was subsequently diagnosed on laparotomy. After closure of the incision without bowel resection, the patient recovered. ASA was stopped on hospitalization but octreotide alone was reinstituted on discharge. Therefore, the patient was treated with more than three months of ASA therapy while also on octreotide. While undergoing treatment from December 2002, the patient received one transfusion of two units of packed red blood cells (PRBCs) in early January 2003. Before treatment, she had received 48 units of PRBCs on 24 occasions dating back to March 2000 (Figure 2). In August 2003, octreotide and erythropoietin were discontinued because her hemoglobin level stabilized. Subsequently, her hemoglobin level fell by 2.5 g/L, but her renal function also deteriorated and erythropoietin, but not octreotide, was restarted. No transfusions were required after January 2003. She died of uncontrollable Staphylococcus aureus sepsis originating from a hip and knee infection, and complications of a sacral skin ulcer in February 2004.

CASE 3

A 68-year-old woman with valvular heart disease, who had undergone aortic and mitral valve replacement surgery in 1997, presented with recurrent melena in 2002. She had been on anticoagulation therapy since 2001. At that time, she required tricuspid valve replacement and closing of a secundum type atrial septal defect. Her medical history included type 2 diabetes mellitus, asymptomatic gallstones and nonalcoholic steatohepatitis. Later, she developed atrial fibrillation and coronary artery disease.
Results of investigations were consistent with iron deficiency anemia. Initial gastroscopy at that time revealed two small prepyloric ulcers, and stomach biopsies demonstrated chronic active gastritis, with evidence of a *Helicobacter pylori* infection. Triple regimen therapy for eradication of *H pylori* was initiated, with an additional two months of proton pump inhibitor. Despite this, the patient continued to experience recurrent episodes of melena and have increased blood transfusion requirements. She required 11 units of PRBCs over a period of five months. Two other gastroscopies were performed the same year, one of which showed a vascular abnormality consistent with angiodysplasia. Colonoscopy also revealed an area with vascular blush perceived to be an angiodysplasia in the descending colon, for which argon plasma coagulation was performed. No biopsies were taken from either site.

The patient was started on octreotide in December 2002, with two weeks of subcutaneous doses of 100 μg twice daily; this was subsequently changed to the daily equivalent dose of the long-acting form of 20 mg once every four weeks. Blood transfusion requirements over the course of six months declined (apart for a one-month period in which the patient stopped taking her medication and required four units of PRBCs). Subsequently, the effect of octreotide began to decrease. Anticoagulation treatment, which was continued by necessity, was more difficult to control. At the end of May 2003, octreotide was discontinued due to perceived failure (Figure 3).

Repeat colonoscopy and enteroscopy with attempted coagulation were performed; however, bleeding subsequently recurred without an observable difference in time delay. In September 2003, long-acting octreotide 30 mg intramuscular was restarted because of apparent increased bleeding (Figure 3). Despite diminished transfusion requirements, again, bleeding did not stop and long-acting octreotide was abandoned in early 2004. A CE study of the small bowel revealed several AEs in the jejunum, with at least one bleeding. A third enteroscopy failed to confirm the bleeding vessel in the jejunum; consequently, the scheduled coagulative therapy was not performed. Due to subsequent overt bleeding, an abdominal angiogram was performed in September 2004 (Figure 4A) that demonstrated a 10 cm segment of the proximal small bowel with hypervascularity and increased capillary blush, and increased arteriovenous shunting with early opacification of the draining vein. Active bleeding from the area was demonstrated with extravasation, and adequate embolization of the feeding vessel was performed using 1 cm microcoils (Figure 4B). However, bleeding was controlled for only six weeks. Transfusion requirements increased through to February 2005, for a total of 10 units of PRBCs. Tranexamic acid 1 g per oral daily was initiated in January 2005, and two months later, subcutaneous octreotide 100 μg three times daily was added. No further transfusions were required from March 2005 to March 2006. Bleeding, however, recurred after this date. Thalidomide 50 mg orally per day was started and added...
to the patient’s existing regimen in late November 2006. After initial mild dizziness, the patient tolerated the dose but it was never increased. She was free from significant gastrointestinal bleeding and transfusions for 23 months thereafter. Her mean (± SD) hemoglobin level in the first six months of 2008 was 120±6.38 g/L (Figure 5). Both iron and coumadin therapy were continued. Tranexamic acid was discontinued in June 2007, and octreotide was stopped in April 2008. A stop date for thalidomide was not determined; however, it would have been discontinued if serious side effects occurred.

A summary of demographic and clinical outcomes of the three patients while on long-acting octreotide is shown in Table 1. In each case, the cause of bleeding could have been modified by other variables; nevertheless, octreotide therapy may have reduced monthly transfusion requirements, raised monthly mean hemoglobin levels and lengthened the interval between transfusion requirements.

The side effects of pharmaceutical treatments were mild except for the development of deep vein thrombophlebitis while on hormones. Side effects with other drugs included

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**Figure 5** Distribution of transfusions of packed red blood cells (PRBCs) and hemoglobin with addition of tranexamic acid 1 g four times daily is shown. Subcutaneous (sc) octreotide was added two months later. However, because of further bleeding, thalidomide was also added in November 2006. Transfusion requirements were reduced, then completely eliminated. Hemoglobin level was maintained thereafter.

**TABLE 1** Demographic features of three patients treated with intramuscular (IM) octreotide long-acting release

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age, years</th>
<th>Symptoms</th>
<th>Site of bleed</th>
<th>Concomitant disease</th>
<th>Previous therapy</th>
<th>Months off Rx, n</th>
<th>Tf off Rx/mo, n</th>
<th>Mean Hg off Rx, g/L</th>
<th>ΔTf off Rx</th>
<th>Months on Rx, n</th>
<th>Tf on Rx/mo, n</th>
<th>Mean Hg on Rx, g/L</th>
<th>ΔTf on Rx, days</th>
</tr>
</thead>
<tbody>
<tr>
<td>1*</td>
<td>76</td>
<td>Melena occult bleed Anemia</td>
<td>AE in colon (possible esophageal source)</td>
<td>Hypertension</td>
<td>Estrogen-progesterone Attempted EGD</td>
<td>12</td>
<td>1.6</td>
<td>75.5</td>
<td>47.9</td>
<td>20</td>
<td>13</td>
<td>0.4</td>
<td>102.3</td>
</tr>
<tr>
<td>2</td>
<td>82</td>
<td>Obscure occult bleed Anemia</td>
<td>Unknown, suspected AE (acetylsalicylic acid was confounder)</td>
<td>Valvular heart disease, chronic interstitial pneumonitis. Chronic renal failure, type 2 diabetes mellitus on acetylsalicylic acid with gastroprotection</td>
<td>Erythropoietin</td>
<td>12</td>
<td>2.1</td>
<td>90.6</td>
<td>27.7</td>
<td>10</td>
<td>8</td>
<td>0.17</td>
<td>108.6</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>Melena occult bleed Anemia</td>
<td>Small bowel and AE (proven bleeding)</td>
<td>Replaced metal aortic and mitral valve. Type 2 diabetes mellitus on coumadin</td>
<td>Attempted EGD</td>
<td>7</td>
<td>2.4</td>
<td>82.3</td>
<td>18.3</td>
<td>20 then 30</td>
<td>13</td>
<td>1.1</td>
<td>100.5</td>
</tr>
</tbody>
</table>

All three women had an introductory week of subcutaneous octreotide in increasing doses to 100 μg twice daily. *Patient presented with dysphagia due to esophageal cancer 22 months after initial presentation. AE Angioectatic vessels; EGD Electrocautery with endoscopy; Hg Hemoglobin; mo Month; Rx Therapy; Tf Transfusions

A summary of demographic and clinical outcomes of the three patients while on long-acting octreotide is shown in Table 1. In each case, the cause of bleeding could have been modified by other variables; nevertheless, octreotide therapy may have reduced monthly transfusion requirements, raised monthly mean hemoglobin levels and lengthened the interval between transfusion requirements.

The side effects of pharmaceutical treatments were mild except for the development of deep vein thrombophlebitis while on hormones. Side effects with other drugs included
abdominal cramps and diarrhea with octreotide, both of which resolved early (within three weeks of starting the medications). The main side effects in cases 1 and 2 were pain at the injection site of the long-acting intramuscular octreotide. Difficulty in controlling glucose was an initial concern in cases 2 and 3. Control of international normalized ratio (INR) in case 3 appeared to be more difficult on octreotide and, in fact, her overt bleeding episodes appeared to be precipitated by a higher than therapeutic INR. There were no side effects with tranexamic acid. In case 3, mild dizziness resolved with the use of thalidomide. No significant side effects with thalidomide were noted during the ensuing 23 months.

**DISCUSSION**

Our report describes three cases of chronic obscure bleeding in which pharmacological therapy had an important impact. Cases 1 and 2 were encountered just before CE became available and did not, therefore, have the benefit of this diagnostic modality. Colonoscopy did, however, reveal nonbleeding AEs.

Initial therapy was attempted with the use of estrogens but led to thrombophlebitis that required anticoagulation for six months. While warfarin could have potentiated bleeding, anemia continued beyond its use. Unfortunately, 22 months into the treatment of the patient in case 1, esophageal adenocarcinoma was diagnosed. It is highly unlikely, however, that the initial episode of melena was due to an early manifestation of this tumour because the patient had no upper gastrointestinal complaints and gastroscopy should have shown some distal esophageal abnormality; however, she had melena only when the final tumour was diagnosed. The incidence of gastrointestinal malignancy is 0.2% when a patient is diagnosed for recurrent iron deficiency within two years (8). Nevertheless, the finding of a complicating lesion raises the likelihood that it contributed at least, in part, to her anemia. In either case, the lessons learned are that one must be vigilant in patients with long-standing iron deficiency anemia. As well, it seems that medical therapy such as octreotide may reduce bleeding from sources other than AEs (9).

In case 2, the presence of renal failure and valvular heart disease increased the probability of AEs as the cause, even if none were found (10). However, the use of low-dose ASA confounded the diagnosis and likely contributed to the chronic nature of the anemia for several years. Nevertheless, we believe that octreotide played a role in control because bleeding stopped with this drug while ASA was continued for more than three months. Once ASA was discontinued, it was also possible to stop octreotide without incurring further bleeding in the remaining months of the patient’s life. Such an outcome raises the possibility that bleeding was due to nonsteroidal anti-inflammatory drug enteropathy rather than angiodyplasia. The case again serves to emphasize the need for vigilance and that octreotide may have a nonspecific impact on obscure gastrointestinal bleeding.

In case 3, repeated diagnostic investigations revealed multiple bleeding AE vessels. However, despite different therapeutic attempts at coagulation and radiological embolization, we believe that the mandatory anticoagulative therapy for triple valvular heart disease complicated initial efforts to achieve hemostasis. Partial responses were noted with octreotide, then with tranexamic acid, but bleeding was finally controlled for the longest period with the addition of low-dose thalidomide, all in the presence of continued anticoagulation.

Despite confounding diagnoses in two cases, all three were suspected of bleeding from AEs, which were documented in case 2 and confirmed to be bleeding in case 1. These vascular ectasias are the most common cause of obscure bleeding and are characteristic of known predisposing conditions (10-12). Current concepts of AE vessel formation suggest it is due to progressive ‘degenerative changes’ related to chronic, intermittent vascular obstruction in the submucosa (13). The intermittent obstruction leads to local hypoxia and induces vascular growth factors (14). An array of associated medical conditions such as valvular heart disease, cirrhosis, renal failure and coagulopathies may predispose to bleeding (10). An additional hypothesis, suggested by Warkentin et al (15) and supported by a recent study (16), suggests that high shear stress across stenotic valves removes high molecular weight multimers of Von Willebrand factor (VWF), with rapid protelysis of VWF leading to poor thrombus formation. This predisposition, aggravated by the high flow in AE vessels, promotes bleeding after vascular rupture.

Management of AE vessels can be difficult; however, the natural history is such that only approximately 10% of these lesions bleed. Earlier studies (10,12,17) reported that coincidentally found AE vessels did not bleed over a period of two to three years of follow-up. Once there is clinical evidence of AE bleeding, the majority stop spontaneously; however, approximately 50% of AEs rebleed in the next year or more, and bleeding is more likely if multiple transusions were previously required (3,14,17,18). Conventional endoscopic control of bleeding with coagulation leads to recurrence in only 25% of cases over a period of two years (7). Few comparable figures based on multiple studies exist for some of the more recent diagnostic modalities (2). In a review of the topic (3), reference was made to two studies in which CE or push enteroscopy was used for diagnosis and therapeutic intervention. Outcomes of these tests led to an 87% and 69% reduction of bleeding over an 18- to 29-month follow-up period, respectively. In the older literature, surgery was also associated with less rebleeding (17).

Pharmacological therapy can help in reducing transfusion requirements and may be the primary treatment if other options fail. No less than four agents were used to stop bleeding in all three patients described in this paper. While the best studied pharmacological agents are estrogen and progesterone, the outcome of clinical trials failed to provide clear evidence of benefit (6,18,19-21). Hypothetically, hormones stabilize fragile vessels, shorten bleeding time and improve possible coagulation defects (22). Two small, crossover controlled trials (19-21) showed benefit, but two prospective trials (6,19) failed to demonstrate efficacy and introduced the possibility of prohibitive side effects.

The less systematically studied but second most common agent used is the somatostatin analogue, octreotide. Octreotide can be administered as daily subcutaneous injections or as a long-acting intramuscular agent. The theoretical effects of somatostatin/octreotide and why it may be useful in the therapy of bleeding AE vessels in different sites include reduction of intestinal blood flow (23,24), improved platelet aggregation (25), inhibition of neoangiogenesis (26,27), possibly increased VWF (28) and in cases of upper gastrointestinal AE vessels, the inhibition of gastric acid secretion may be relevant (29).
In addition to the three cases reported herein, data regarding 137 other patients have been published, of which 132 were adults and five were children (17 years of age and younger). A single, uncontrolled series of 17 patients (30) suggests that a complete cessation of bleeding was observed in 10 patients (59%), with therapy failing completely in only three (18%). Another series of 17 patients (31) has been published in abstract form only; however, the details are unclear. Since our review (7), the first controlled trial of octreotide given as 50 μg subcutaneous twice daily was published by Junquera et al (32). In this two-year study, the outcome of 32 patients with diagnosed AE vessels was compared with that of 38 oral placebo-treated patients enrolled in a parallel clinical trial. There appeared to be a significant reduction in the need for iron therapy in the actively treated group, and a 22% and 32% difference in rebleeding rate at one and two years, respectively, was observed in the treated group. Three other published cases (33) that used long-acting octreotide reported success with treatment. In an open-label series of 13 patients reported by Scaglione et al (34) using long-acting octreotide, transfusion requirements were significantly reduced over a 12- to 60-month follow-up period. Our experience seems to match that reported by these authors.

The safety profile of octreotide therapy is noteworthy (25,35). More serious effects of long-term octreotide may be related to glucose control in diabetic patients, and formation of gallstones or pancreatic diarrhea due to the inhibition of pancreatic secretions. A theoretical concern also includes a possible effect on myocardial function (36) and induction of pulmonary hypertension with heart failure (37). In addition, we noted initial difficulty in controlling the patients’ INR. Perhaps octreotide-induced slowing of intestinal transit may have increased the absorption of warfarin. Finally, the possibility that tachyphylaxis occurred in case 2 – thereby reducing the effect of octreotide – may need to be considered with this agent.

Initiation with octreotide in the present case series used an induction period of approximately one week to guard against potential side effects. Long-acting octreotide was subsequently used more regularly. Discontinuing octreotide should also be considered. In this context, we think it is reasonable to follow a modified suggested algorithm for hormonal treatment, similar to the one suggested by Van Cutsem and Piessevaux (38). After two to three months, increasing the dose to a maximum of 30 mg intramuscular or the equivalent subcutaneous dose (300 μg three times daily) may be worth trying in initial failures. Treatment can be abandoned if no effect is observed at the maximum dose for two to three months. Alternatively, if treatment is successful, stopping after six months of therapy may be considered and restarting if bleeding recurs. Few data exist regarding chronic AE-related bleeding and the effect of pharmacological therapy (7).

Anecdotal use of tranexamic acid in doses ranging from 4 g/day to 4.5 g/day has been reported as well, mainly in cases of hereditary hemorrhagic telangiectasia (39-41). The antifibrinolytic effects of the drug may also have relevance in diminishing clot dissolution in cases of AE vessels. In case 3, the drug had only partial effect due to the presence of AE vessels and Van Willebrand’s disease controlled with thalidomide. Since its publication, however, two other cases involving patients with bleeding AE vessels and Van Willebrand’s disease controlled with thalidomide in doses of 100 mg/day or 150 mg/day were published (48,49). Response to the addition of thalidomide was so dramatic and prolonged in our case that we are reasonably confident that the drug had the desired effect. However, it is possible that the combination of all three pharmaceutical agents contributed to the effect and allowed the low dose of thalidomide to be effective without the need to increase. To our knowledge, there are no published combination evaluations.

SUMMARY

We report three difficult-to-manage cases of obscure gastrointestinal bleeding in which AE vessels were suspected to be causative. In two cases, however, confounding diagnoses may have been alternative or, at least, contributory causes. The cases illustrate the possible nonspecific hemostatic effect of octreotide and exemplify the need for periodic reassessment of etiology of bleeding when a specific diagnosis of AE is primarily suspected. Finally, case 3 exemplifies the difficulty in the management of patients with complicated bleeding. Thalidomide appears to be a promising and effective drug in the management of such cases; however, controlled trials are eagerly awaited.

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REFERENCES


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