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Hormonal Therapy for GI Angiodysplasia: Out of Hope After Failure of the Scope?

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Abstract

Angiodysplasia of the gastrointestinal (GI) tract can present both diagnostic and therapeutic challenges. Despite the recent advances in endoscopy, many patients continue to suffer from recurrent bleeding. We report a remarkable case of a multi-year history of transfusion-requiring obscure overt recurrent GI bleeding, refractory to multiple endoscopic therapies as well as both octreotide and thalidomide. Upon initiation of hormonal therapy, the patient's bleeding completely resolved, with complete cessation of transfusion and procedure requirements for 18 months. Our case of a remarkable response to hormonal therapy illustrates an unusual but clinically important benefit that may have evaded the results of existing small clinical trials.

Keywords

Gastrointestinal hemorrhage, Melena, Angiodysplasia, Hormone replacement therapy

Introduction

GI angiodysplasia of the small bowel accounts for 30-40% of obscure gastrointestinal bleeding (GIB) and is the most common source of bleeding in patients greater than 60 years old [1]. Recent advances in endoscopy, including double-balloon enteroscopy (DBE) and video capsule endoscopy, have increased the diagnostic and therapeutic potential; however, the diagnostic yield is 75% at best, leaving a quarter of these patients with undiagnosed blood loss[1]. Furthermore, the rebleeding rate following endoscopic intervention is significant, making a pharmacological approach more practical [1].

Case Report

A 76-year-old female was found to have symptomatic anemia in 2000 consistent with chronic GI blood loss. Esophagogastroduodenoscopy (EGD) and colonoscopy revealed extensive diverticular disease and non-bleeding colonic angioectasias. She received transfusion of several units packed red blood cells (pRBCs) but developed recurrent melenic overt GI bleeding in 2007, initially precipitated by a need for aspirin and clopidogrel for severe symptomatic coronary and peripheral vascular disease. She eventually required coronary stenting and femoral-popliteal bypass. Recurrent melenic obscure overt bleeding persisted despite discontinuation of antiplatelet therapy. Endoscopic evaluations revealed diffuse GI angiodysplasia involving gastroduodenum, small bowel, and colon with bleeding identified in multiple different regions of the small bowel on successive capsule endoscopies. Multiple endoscopic therapies were performed via DBE between 2010 and 2013, and she failed therapeutic trials of octreotide in escalated doses (after some benefit with reduced hospitalizations for greater than 1 year) and thalidomide (poorly tolerated and required discontinuation after several months). From June 2012 through October 2013, melenic overt GI bleeding required 14 inpatient admissions, 63 units of pRBC transfusions, and 16 procedures with endoscopic therapy of diffuse small intestinal angioectasias via DBE proving ineffective clinically. In November 2013, hormonal therapy was instituted using estrogen 1.5 mg/norethindrone 30 mcg. Since institution of this therapy, there have been no clinical rebleeding events, hospitalizations, transfusions, or endoscopic procedures, and hematocrit has remained stable over an 18-month period; antiplatelet therapy with aspirin has been successfully resumed without rebleeding.

Discussion

Current consensus regarding medical therapy for gastrointestinal angiodysplasia has focused on somatostatin analogues and thalidomide [1,2]. Somatostatin analogues reduce splanchnic blood flow and downregulate vascular endothelial growth factor (VEGF). Octreotide was shown to endoscopically decrease angiodysplastic lesions in one study [3]. Thalidomide is an antiangiogenic drug that inhibits VEGF at lower doses. Despite case series reporting efficacy in refractory GI angiodysplasia, its use remains limited secondary to frequently experienced side effects (dizziness, fatigue, peripheral neuropathy) [4]. Although the exact mechanism of how hormonal agents induce hemostasis is uncertain, many theories have been postulated. Hormonal therapy increases the number of circulating activated platelets [5], thereby shortening the bleeding time [6]. Estrogen has been shown to increase the vascular reactivity and sensitivity to catecholamines, thereby promoting vasoconstriction [7]. Estrogen also promotes vascular endothelial regeneration and integrity [8]. In addition, raloxifene, a selective estrogen receptor modulator, induces the expression of endoglin and ALK1, which are molecules crucial for endothelial growth [9].

Hormonal therapy was initially proposed after reports showed

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improvement in epistaxis in Hereditary Hemorrhagic Telangiectasia (HHT) during pregnancy [10]. These findings prompted further investigations with hormonal therapy and GIB. In their review, Szilagyi and Ghali [11] noted 22 case reports that showed reduction of bleeding or arrest of bleeding with hormonal therapy. Their analysis [11] on the use of hormonal therapy included four controlled trials and yielded mixed results with limitations including heterogeneity between the studies, potential differences in patients with acute vs chronic bleeding, and differing dosages of estrogen / progesterone. The only double blind, randomized controlled trial [2] of hormonal combination therapy concluded that hormonal therapy was no better than placebo for prevention of angiodysplastic bleeding. While the groups were matched and randomized, this study was limited by small sample size, use of relatively low doses of hormonal therapy, and a placebo group that contained more acute bleeders [12]. The aforementioned double-blinded trial [2] and a controlled trial [13] form much of the basis of a recent meta-analysis [14] regarding medical and endoscopic therapies for angiodysplasia, which concluded that continuous hormonal therapy was not effective for preventing angiodysplastic bleeding.

Limitations of available studies include small sample sizes, which preclude subgroup analyses (gender, age, location of angiodysplasia) and use of lower doses of estrogen than previously shown effective in case reports. Ross et al [15] have previously suggested that obscure GIB from distal small bowel angiodysplasia responds to hormonal therapy and may respond differently than lesions in other parts of the GI tract. Our case demonstrates an unequivocal and dramatic response to hormonal therapy after years of troubling, recurrent small bowel angiodysplastic bleeding refractory to medical and endoscopic management. Moreover, it demonstrates an unusual but clinically important benefit that may be missed by clinical trials that may be underpowered.

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