Rectosigmoid colon venous malformation successfully treated with propranolol and celecoxib

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ABSTRACT

Venous malformations are the most common kind of vascular malformations and are a result of errors in vascular morphogenesis [1]. Bleeding is the most common symptom of gastrointestinal (GI) vascular malformation [2]. Various treatment modalities are available, including endoscopy to destroy vascular malformations by sclerotherapy with ethanol, therapeutic angiography with selective embolization, especially for acute hemorrhage, and surgery [1]. When these interventions are not possible, are contraindicated or have been ineffective, as often happens in patients with multiple lesions distributed across several segments of the digestive tract or when the lesion is widespread, or when the patient has comorbidities that prevent the use of invasive procedures, pharmacological treatment is the only possible alternative [3,4]. We report here a case of rectosigmoid colon venous malformation that was successfully treated with propranolol and celecoxib.

1. Case report

A 19-year-old female was hospitalized due to melena and severe anemia. Her Hb level was 4.9 g/dl. No one else in her family had similar problems. She had had hemorrhoids since she was 3 years old. When she was 5 years old, she was referred to our hospital with a pale complexion. Her Hb was 4.2 g/dl. A perirectal vascular lesion was found by computed tomography (CT) and magnetic resonance imaging (MRI). Laparoscopic resection of the pelvic lesion was performed, and the diagnosis was perirectal venous malformation. A residual lesion was found by postoperative MRI. When she was 13 years old, bleeding increased again, and hemorrhoidectomy and resection of the venous malformation were performed. After the operation, the bleeding improved and was only seen in the case of constipation. However, the bleeding got worse again when she was 19 years old.

The patient did not have thrombocytopenia or a clotting disorder. A thickened rectal wall (Fig. 1) and phleboliths around the rectum that suggested widespread venous malformation were observed by enhanced CT examination (Fig. 2). Dilated veins...
connected to an internal hemorrhoid were evident by colonoscopy (Fig. 3). Neither surgical resection nor sclerotherapy was indicated because the lesion showed high blood flow and occupied a broad area around her rectum. Surgical resection would also require colostomy.

On day 17 of admission, Octreotide was initiated at 40 mcg/day and then increased to 54 mcg/day. However, bleeding continued and there was no decrease in the quantity of red blood cell (RBC) transfusions, which were required every 3 days. Twenty-two units of RBC were transfused in the first month of admission. She was referred to our department for further treatment. In the 5th week of hospitalization, we started propranolol at 0.5 mg/kg/day. Although the Hb level increased to 9–10 mg/dl after the initiation of propranolol, bleeding continued. Celecoxib, which was started to treat her knee pain, was found to be predictably effective, and therefore was administered regularly. Propranolol and celecoxib were gradually increased to 2.7 mg/kg/day and 9.0 mg/kg/day, respectively. The rectal bleeding gradually decreased and anemia improved. She received 18 and 8 units of RBC in the 2nd and 3rd months of admission, respectively. Once she was discharged, her anemia got worse again and she required an additional 6 units of RBC in the 4th month, probably due to increased daily activity. Five months after the initiation of propranolol and celecoxib, she could maintain Hb at 15 g/dl without transfusion, although d-dimer has been high as 7.4–13.4 µg/ml (<1.0) which indicate a consumption.

2. Discussion

In cases in which endoscopy, therapeutic angiography or surgery is not indicated, pharmacological treatment is the only alternative therapy for GI vascular malformation. Estrogen-progesterone, thalidomide and octreotide have been used as prophylaxis for hemorrhage due to GI vascular malformation [5].

Estrogen-progesterone has been used to control obscure GI bleeding in patients with vascular malformation. The mechanisms of action are vascular stability, improved coagulation, decreased mesenteric blood flow. But they have not been found to be uniformly successful and are controversial. Equally important is that hormones are associated with some significant side effects [5].

High concentrations of VEGF are associated with aberrant angiogenesis and the formation of vascular malformations with a thinner muscle layer, which causes high vascular fragility and a tendency to hemorrhage [6,7].

Thalidomide can inhibit VEGF, which is the rationale for its use to treat vascular malformation. A randomized trial that compared treatment with thalidomide with iron supplementation in 55 patients showed a significant reduction in bleeding episodes. The response rate in the thalidomide-treated group was 71.4% compared to only 3.7% in the control group. That trial also demonstrated a significant decrease in serum levels of VEGF in the treatment group [7]. However, thalidomide must not be used in women with child-bearing potential because of teratogenesis. Therefore, thalidomide was not an option for our patient. Octreotide is another drug that can inhibit angiogenesis, constrict splanchnic vessels, increase vascular resistance and increase platelet aggregation [8]. A meta-analysis of 3 prospective studies with a total of 62 patients showed a 76% response rate [8]. Therefore, we used this drug as the first-line therapy. Unfortunately, our
patient did not respond well. This was why she was referred to our department to seek alternative treatments.

Propranolol has become a valuable drug for the treatment of hemangiomas. Propranolol also has effects such as vasoconstriction, blocking of angiogenesis through its effects on VEGF, and induction of apoptosis [9]. A recent randomized study demonstrated that 88% of infantile hemangioma patients who received a propranolol regimen showed improvement by week 5 [10]. There is evidence that propranolol is effective in the treatment of lymphatic malformations that fall into vascular malformation [11]. Our patient did not show a clear response, probably due to widespread vascular malformation.

However, she did show a response with the addition of celecoxib. It has been demonstrated that celecoxib can inhibit angiogenesis due to the inhibition of VEGF expression in an animal model [12]. There has been no previous report that celecoxib is effective for the treatment of vascular malformation in a clinical setting.

The combination of propranolol and celecoxib might be useful for controlling massive bleeding from large intractable vascular malformation without adverse events. The synergistic mechanisms of propranolol and celecoxib should be clarified.

3. Conclusions

Sclerotherapy, therapeutic angiography, surgery and traditional pharmacological treatment were not available in this case. The combination of propranolol and celecoxib was effective for controlling bleeding from venous malformation without adverse events.

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