Intractable anemia due to extensive refractory angiodysplasia of the small intestine stabilized by an anti-angiogenic agent

Anémie incontrôlable en rapport avec des angiodysplasies réfractaires de l’intestin grêle stabilisée par un traitement antiangiogénique

Angiodysplasia (AD) of the small bowel is the most frequent etiology of otherwise unexplained gastrointestinal bleeding and chronic anemia after negative endoscopic screening, as usually demonstrated by wireless capsule endoscopy (WCE). Main known risk factors are chronic renal failure, aortic sclerosis and von Willebrand disease. Endoscopic electrocoagulation is the treatment of choice, with a variable rate of success. Treatment of refractory cases is not well defined but the roles of splanchnic blood flow moderators as octreotide and that of anti-angiogenic drugs as thalidomide or bevacizumab, an antibody against vascular endothelial growth factor (VEGF), have recently been highlighted [1]. We here report a case of intractable anemia due to extensive refractory AD of the small intestine, eventually treated with success via bevacizumab.

Case report

A 47-year-old woman with iron deficiency anemia for over 12 years was referred to our hospital unit in 2014. Past history included hypertension, diabetes mellitus and active smoking up to 33 pack-years. She had neither anticoagulant nor antiagregant therapies. Endoscopic and radiological explorations (WCE and angioscan) had led to the diagnosis of multiple jejunal angiodysplasia. Hereditary hemorrhagic telangiectasia (HHT) and other disorders of coagulation or conditions that feature high shear stress had been investigated and excluded. Intravenous iron supplementation had been administered as first line therapy. In 2005, red blood cell transfusion had been started with increasing blood supply demand overtime. From 2005 to 2014, the patient had undergone 7 endoscopic argon plasma coagulation interventions. In 2011, long acting release-octreotide (20 mg/month over 6 months) had failed to reduce the blood transfusion needs. In 2013, 100 mg/day thalidomide had been initiated although side effects had led to discontinuation after 3 weeks. When she was referred to us in 2014, transfusions were so frequent that surgical therapy was offered to our patient who underwent partial jejunal resection of the first 50 cm of the jejunum, where AD were too numerous to be electro-coagulated. Intraoperative examination of small bowel revealed no vascular or digestive abnormalities; histology confirmed no more than multiple AD. Unfortunately, blood transfusion needs remained unchanged as WCE showed extensive beyond the resected segment. By October 2014, our patient had been blood transfused 355 times. For those reasons and by analogy with HHT, bevacizumab (5 mg/kg once every 2 weeks) administration was initiated. Over the 3-month-treatment duration, hemoglobin level rose to 126 g/L without any blood transfusion (figure 1). An asymptomatic glomerular syndrome with proteinuria of 2 g/day arose but regressed at bevacizumab discontinuation. WCE revealed persistence of non-hemorrhagic AD. Two
months later, recurrence of bleeding led to resume bevacizumab administration at a maintenance dose of 400 mg once per month. The patient has been asymptomatic since then, featuring a stable and isolated proteinuria treated with ramiprilate. Moreover, WCE of December 2015 displayed a dramatic reduction of angiodysplasia.

**Discussion**

This case illustrates the difficulty in successfully managing intratable digestive hemorrhage from refractory small bowel AD, especially when the disease cannot be classified like the one of our patient. Physiopathology of AD is not entirely understood although the central role of VEGF in angiogenesis dysregulation has been put forward [2]. In HHT, bevacizumab is reported to be an alternative treatment to liver transplantation as it led to restoring a normal cardiac output in cases of severe hepatic vascular malformations [3]. It also positively affected quality of life by reducing epistaxis although efficiency is dose-related [4]. Similar effects have also been described in the case of a patient bearing AD related to Glanzmann thrombasthenia [5]. We hypothesize that bevacizumab affects capillaries, by correcting mural cell coverall and vessel integrity in the short-term, which agrees with the post-treatment WCE findings (i.e. persistence of non-hemorrhagic AD and reduction of new AD).

**Conclusion**

This case highlights the positive effect of anti-VEGF antibody on refractory digestive AD. This promising result has to be moderated since it only persists during treatment and exposes the patient to side effects of anti-angiogenic drugs.

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**References**


