

Thalidomide as treatment for digestive tract angiodysplasias

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ABSTRACT

An 80-year-old man with von Willebrand's disease was admitted with severe melaena. Despite suppletion with von Willebrand concentrate he continued to be dependent on blood transfusions. Endoscopic examination did not show a bleeding focus. Video capsule endoscopy showed active bleeding from angiodysplasias in the proximal section of the small intestine. Ultimately, treatment with thalidomide was initiated at a dose of 100 mg/day. Soon after starting treatment his stools became normal and his haemoglobin level stabilised. No bleeding problems occurred for 11 months, after which the thalidomide treatment was stopped because of the potential side effects. Two months later he again developed melaena and treatment with thalidomide was restarted with a successful outcome. Trying to lower the dose to 50 mg resulted in rebleeding after three months with stabilisation after increasing the dose to 100 mg again. Monotherapy with thalidomide improves the clinical picture but may not be sufficient in the long term. Additional therapy, such as argon plasma coagulation or the use of the novel drug lenalidomide, might be necessary.

KEYWORDS

Angiodysplasias, gastrointestinal bleeding, thalidomide

INTRODUCTION

Blood loss from the upper digestive tract is a common problem. Frequently, bleeding from ulcers in the stomach or the duodenum or from reflux oesophagitis is observed. Angiodysplasias or arteriovenous malformations are seldom the cause of bleeding. Angiodysplasias or arteriovenous malformations are mainly found in the small bowel, especially in the lower ileum.^{1,2} At present the treatment

of choice is endoscopic intervention with argon plasma coagulation. This treatment is not always possible, especially when angiodysplasias are located in the lower section of the small bowel. A new but to date not frequently used therapy in these patients is treatment with thalidomide. Recently we saw a patient with severe gastrointestinal blood loss due to angiodysplasias and von Willebrand's disease type II-a who was successfully treated with thalidomide.

CASE REPORT

An 80-year-old man was admitted to our hospital with severe melaena in May 2004. As a child he had had poliomyelitis; furthermore he had documented von Willebrand's disease type II-a and a bleeding duodenal ulcer was diagnosed 50 years ago. Three years before this admission he had been examined for black coloured stools for which no explanation was found at that time.

On presentation he admitted having black coloured stools and had experienced progressive fatigue over the past few days. He was not on oral anticoagulation or NSAIDs. On physical examination we saw a tired patient with a blood pressure of 160/60 mmHg, a regular heart rate of 80 beats/min and a peripheral saturation of 99%. Abdominal examination was normal. Rectal digital examination showed black/brown faeces. Laboratory results showed a haemoglobin level (Hb) of 5.4 mmol/l (8.5 to 10.9 mmol/l) and a mean corpuscular volume (MCV) of 81 fl. (80 to 100 fl). Iron level was 5 µmol/l (10 to 25 µmol/l), ferritin 12.0 µg/l (20.0 to 250.0 µg/l) and transferrin 2.86 g/l (2.00 to 4.00 g/l) with 7% iron saturation. Platelet counts were normal. Additional work-up (gastroscopy, colonoscopy, computed tomography scan of the abdomen and enteroclysis of the small bowel) did not show a focus for his bleeding. During admission he remained dependent on blood transfusions. Treatment with tranexamic acid was initiated

with transfusion of a total of 20 units of red blood cells (RBC) and three units of fresh frozen plasma (FFP). As treatment of his von Willebrand's disease desmopressin (DDAVP) was infused. Finally his haemoglobin level became stable and the patient could be discharged.

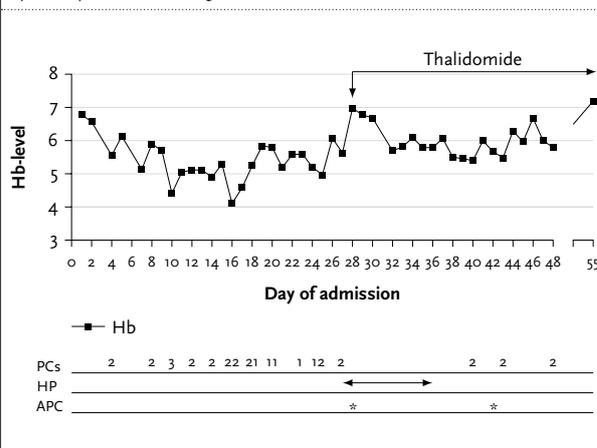
Late July 2004 he was readmitted with complaints of fatigue and an Hb level of 3,5 mmol/l. Examination of the faeces for occult blood turned out to be positive. Again additional endoscopic examination failed to localise the bleeding, although gastroscopy did show oozing blood in the pars descendens of the duodenum. A Meckel's scan was negative. During this admission he was again treated with tranexamic acid, DDAVP and a total of 15 units of RBCs and one unit of FFP. Because of the persistent bleeding without an obvious focus he was transferred to Leiden University Medical Centre. The next day a video capsule endoscopy showed several angiodysplasias in duodenum and jejunum which were not actively bleeding. Because he did not respond to DDAVP he was treated with von Willebrand's factor concentrate (HaemateP), in addition to RBC. Again stabilisation occurred.

In September 2004 he was readmitted with the same problem. Video capsule endoscopy showed fresh red blood in the duodenum and upper jejunum. Argon plasma coagulation intervention (double balloon endoscopy was not available at that time) was not successful so treatment with thalidomide (100 mg/day) was initiated. Five days after commencing thalidomide treatment, our patient started passing normal coloured stools. Two weeks after starting treatment, the patient again developed melaena. Again there was active blood loss from an angiodysplasia in the duodenum. A single argon plasma coagulation was performed, after which the Hb level stabilised (figure 1). During treatment with thalidomide during the next 11 months our patient remained free of symptoms with a stable Hb level. He was examined several times by a neurologist and several electromyograms were performed. No (progressive) neurological problems were found, although interpretation was hampered due to the documented poliomyelitis in the patient's history. Because of the potentially severe side effects of thalidomide, especially the neurotoxicity, and the poliomyelitis in the patient's past, the decision was made to stop the thalidomide treatment in August of 2005.

Two months later he again experienced melaena with complaints of fatigue, and a low Hb level. The possibility of performing a double balloon endoscopy was discussed. He refused further endoscopic treatment. Therefore, he was again treated with thalidomide (100 mg/day) with instant success (figure 2). At the time of his first outpatient control in February 2006 the patient was free of symptoms with an Hb level of 8,5 mmol/l. Trying to lower the dose to 50 mg resulted in rebleeding in May 2006 with stabilisation after increasing the dose to 100 mg again.

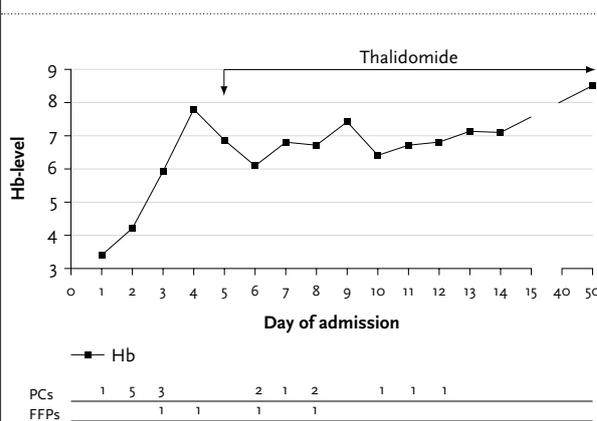
In July 2006 he was readmitted with rebleeding despite the use of thalidomide 100 mg/day. Gastroscopy showed

Figure 1. Admission September 2004: course of Hb in mmol/l, time of blood transfusion (PCs), treatment with HaemateP (HP), argon plasma coagulation (APC) and start of treatment with thalidomide



The patient became independent of blood transfusions with a stable Hb level after starting treatment with thalidomide.

Figure 2. Admission December 2005: course of Hb in mmol/l, time of blood transfusion (PCs), fresh frozen plasma (FFPs) and time of restarting treatment with thalidomide



The patient became independent of blood transfusions with a stable Hb level after restarting treatment with thalidomide.

active bleeding from an angiodysplasia in the jejunum. A single argon plasma coagulation was performed and the thalidomide dose was increased to 150 mg/day. In the near future he may be put on a similar drug, lenalidomide.

DISCUSSION

Angiodysplasias are newly formed blood vessels in the mucosa of the bowel. They can be part of several syndromes such as the Klippel-Trenaunay-Weber syndrome, the syndrome of Ehlers-Danlos, the CREST variation of scleroderma and the inheritable haemorrhagic

telangiectasia. They also occur sporadically, especially at higher age, and can be associated with considerable morbidity. Chronic mucosal ischaemia may play a role. The most frequently observed angiodysplasias are found in the colon, but they also occur in the small bowel, with a location preference for the lower ileum.^{1,2} The standard treatment at present is argon plasma coagulation. Hormone treatment with oestrogens used to be used;^{3,4} however, the effect of this treatment is at best doubtful.⁴

Thalidomide (also known as Softenon) was used between 1950 and 1970 as a sleeping pill and an antiemetic drug during pregnancy. At the end of the 1960s its use was abandoned worldwide due to severe teratogenic effects.^{5,7} However, during the past few years thalidomide has been shown to be effective in a number of diseases: multiple myeloma,⁸ erythema nodosum leprosum,⁹ Behçet's disease,¹⁰ graft-versus-host disease in allogenic bone marrow transplantation,¹¹ Crohn's disease,^{12,13} HIV-wasting syndrome in AIDS patients and stomatitis aphthosa in HIV patients.^{14,15} The effect of thalidomide is also being evaluated in other forms of cancer, such as renal-cell carcinoma, glioblastoma multiforme and Kaposi sarcoma.¹⁶⁻¹⁸

Thalidomide is on the list of 'orphan drugs' of the European Agency for the Evaluation of Medicinal Products (EMA) for the treatment of multiple myeloma and erythema nodosum leprosum and is a non-registered drug in the Netherlands. The exact working mechanism of thalidomide is as yet unknown but considering the success in the treatment of the various disorders mentioned above it is likely that thalidomide has anti-inflammatory, immune-modulating and antiangiogenic properties. Especially this last feature seems to be important in the treatment of multiple myeloma.⁸ Besides its anti-inflammatory effects by suppression and modulation of the production of multiple cytokines, such as TNF- α in diseases like Crohn's disease,^{19,20} thalidomide can also inhibit angiogenesis, which is probably most important in the treatment of angiodysplasias.²¹ This inhibition most likely takes place through two pathways. First the suppression of the production of vascular endothelial growth factor (VEGF) plays an important role.²² Serum VEGF is greatly increased when angiodysplasias of the colon are present.²³ Because VEGF is an important angiogenic factor in the development/growth of cancer cells and normal cells in hypoxaemic circumstances,²⁴ VEGF could play an important role in the pathophysiology of angiodysplasias.²⁵ Especially in elderly patients, hypoxaemia of the mucosa cells of the bowel might induce the forming of angiodysplasias through production of VEGF. Secondly, thalidomide inhibits the transcription factor NF- κ B, which plays a role in apoptosis. It is thought that a metabolite of thalidomide is able to inactivate NF- κ B and subsequently slows the growth of cells and induces apoptosis.²⁰

In the literature a relation has been suggested between the occurrence of angiodysplasia and the presence of severe aortic

stenosis,²⁶⁻²⁸ which could not be confirmed by systematic prospective investigations.^{29,30} In some patients a dramatic clinical improvement was observed after replacement of the stenosed aortic valve. On physical examination there were no signs of aortic stenosis in our patient. Warkentin *et al.* suggested a relation between acquired von Willebrand's disease type II-a, aortic stenosis and angiodysplasia.^{31,32} Our patient had documented congenital type II-a von Willebrand's disease and the possible contribution of an acquired aggravation is only speculative.

Recently, the use of thalidomide in refractory gastrointestinal bleeding due to angiodysplasias was reported.^{25,33} The 2004 article in *Gut* described three patients with severe gastrointestinal bleeding of the small bowel, at least one of whom had video capsule endoscopy proven angiodysplasias of the jejunum and ileum. All three patients were treated with thalidomide (100 mg/day) for four months. In all these patients the bleeding stopped within two weeks after the onset of treatment. Despite the limited follow-up, the effect of thalidomide treatment seemed to have lasted 22 to 33 months, during which no blood loss was observed. A recent case report described a 54-year-old patient with von Willebrand's disease II-b and angiodysplasia, who was successfully treated with thalidomide at a dose of 150 mg daily with a follow-up of six months.³⁴

Our patient was also free of symptoms soon after (re)starting the thalidomide. In 2004 the combined effect of the argon plasma coagulation of the angiodysplasia in the duodenum and thalidomide initially stopped the bleeding successfully. Later on, the 11-month period without bleeding and the success after restarting the thalidomide in 2005 proved the thalidomide to be effective. After this initial success the most recent rebleeding indicates that monotherapy with thalidomide improves the clinical picture but may not be sufficient in the long term. Additional therapy such as argon plasma coagulation or the use of the novel drug lenalidomide might be necessary. Due to the side effects of thalidomide, such as sleepiness, dizziness, constipation and especially peripheral neuropathy, the compliance of this drug is not very good.^{35,36} The use of adequate laxatives and strict neurological control is necessary when using this drug. A new thalidomide-like drug (lenalidomide) is believed to be more potent than thalidomide with possibly less side effects. The first results of this drug in patients with multiple myeloma are encouraging.^{37,38}

CONCLUSION

Angiodysplasias of the digestive tract can cause severe blood loss. It is not always possible to treat these bleeds by endoscopic intervention and local haemostatic procedures. Case reports of treatment with thalidomide show that this

drug offers a treatment option in patients with difficult to treat gastrointestinal blood loss due to angiodysplasias. It is assumed that the effect of thalidomide is based on inhibition of the VEGF production and inactivation of NF- κ b. Unfortunately, the use of this drug is limited due to the side effects, especially neurotoxicity, and it may not be sufficient as monotherapy in the long term. Perhaps the more potent successors of thalidomide which cause less side effects, such as lenalidomide, will offer a solution for these problems in the future.

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