BMJ Case Reports

Novel treatment (new drug/intervention; established drug/procedure in new situation)

Successful treatment of bleeding gastro-intestinal angiodysplasia in hereditary haemorrhagic telangiectasia with thalidomide

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Summary

Hereditary haemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterised by epistaxis, cutaneous telangiectasia and visceral arterio-venous malformations (AVMs). It affects approximately one in 5000 people. Control of sustained and repeated haemorrhages from telangiectasias in the nose and gut in patients who may be transfusion dependent is clinically challenging. After repeated endoscopic coagulations, multiple lesions often recur at other sites of gastro-intestinal tract, where endoscopic therapy or surgical resection is not possible. Hormonal therapy has been employed for more than 50 years but has recently been shown to be ineffective. Thalidomide, with its antiangiogenic mechanism of action, seems to be promising drug as a treatment option where other modalities have been unsuccessful. In this article, the authors discuss a novel treatment of bleeding gastro-intestinal angiodysplasia.

BACKGROUND

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease is an autosomal dominant disorder characterised by epistaxis, cutaneous telangiectasias and visceral arterio-venous malformations (AVMs). It affects approximately one in 5000 people.[1 2] The characteristic lesions in this disorder are angiodysplasias that consist of focal dilatations of postcapillary venules and AVMs. These malformations are thin walled, fragile vessels, lacks smooth muscle cells, susceptible to rupture[3] and bleed often recurrently and in such a severity as to require blood transfusions. These angiodysplasias are characterised by elevated serum levels of vascular endothelial growth factor (VEGF)[4] and basic fibroblast growth factor, both of which are angiogenic. Suppressing VEGF (antiangiogenic) may lead to disruption in the pathogenesis behind these pathological vessels, which may be useful in treating bleeding angiodysplasias. Thalidomide is one such drug.[5]

Thalidomide was first introduced as a treatment for morning sickness in Europe in 1950s, but was withdrawn due to its severe teratogenic effects.[6] More recently, the

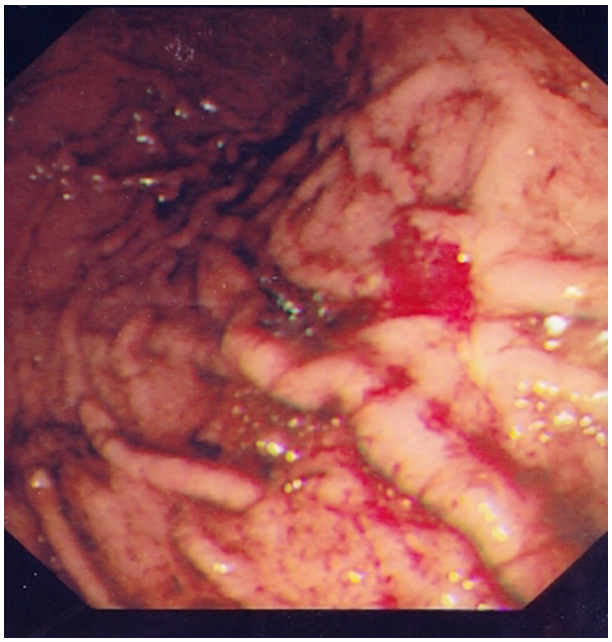

Figure 1 Oesophago-gastro-duodenoscopy showing gastric angiodysplasia.

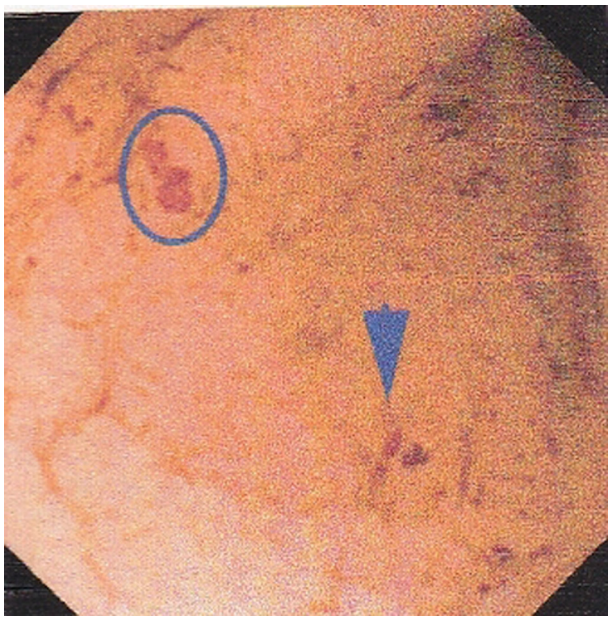

Figure 2 Capsule endoscopy showing angiodysplasias.

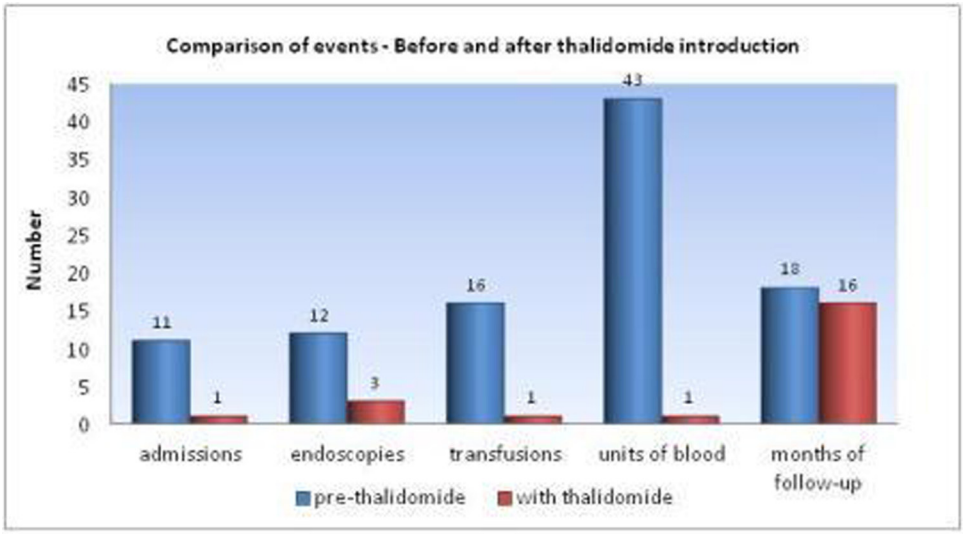

Figure 3 Comparison of events – before and after thalidomide introduction.

antiangiogenic property of thalidomide has shown benefit in treating angiodysplasias.

In this report, we describe a case of recurrent bleeding angiodysplasia successfully treated with thalidomide without significant treatment related toxicity.

CASE PRESENTATION

A 77-year-old frail lady with background history of congestive cardiac failure, atrial fibrillation but not on anticoagulation was admitted in 2006 to medical assessment unit with symptomatic anaemia presenting with malaise and decreased exercise tolerance. She has been previously found to be anaemic by her General Practitioner and was taking ferrous sulphate. She was diagnosed with HHT in 1990 and also had a family history of this disorder. Her admission haemoglobin was 5.8 g/dl with MCV 76 fL, ferritin 7.5 µg/l (normal 15–250) and was transfused four units of packed cells. An oesophago-gastro-duodenoscopy showed gastric and duodenal angiodysplasias. Colonoscopy complete to Caecum was normal. Over the next 18 months, she was admitted on 11 occasions with symptomatic anaemia and malaena and had to be transfused with 44 units of packed cells. During this period, she had numerous endoscopies (upper and lower) as well as capsule endoscopy, which revealed gastric and small bowel angiodysplasias (figures 1 and 2). Frequent argon plasma coagulation were carried out for gastric and duodenal angiodysplasias however she was not fit for double balloon enteroscopy in view of her frailty and sedation risks. She was prescribed hormonal therapy (ethylestradiol 100 mcg OD) and antifibrinolytic agent (tranexamic acid 500 mg three times a day) without any benefit.

At this point, she was started on thalidomide 100 mg OD following discussion with tertiary unit. There was considerable symptomatic improvement. She required one unit of transfusion in immediate 8 week follow-up period but remained free from transfusion for further 14 months. Thalidomide dose was maintained at 100 mg throughout her entire 16 months follow-up period. Her most recent haemoglobin was 13.0 g/dl. Since thalidomide, she had significant reduction in hospital admissions, number of endoscopies performed and transfusion requirement, which are illustrated in figure 3 below. She also had better quality of life without any treatment related side-effects.

DISCUSSION

We report a case of recurrent bleeding angiodysplasia effectively treated with thalidomide. A variety of hormonal treatments and antifibrinolytic agent have shown promise in small studies for management of bleeding secondary to AVMs in patients with HHT. They include oestrogen preparations like tamoxifen, danazol, octreotide, desmopressin, ethinylestradiol and high dose tranexamic acid.[7–13] These therapies have not been supported by data from randomised controlled trials.[14] Our patient did not respond to either of these treatments.

There has been much excitement about case reports following use of angiogenesis inhibitors like thalidomide and lenalidomide.[15–17] Small clinical trials have shown some benefit but requires further experience with angiogenesis inhibitors in HHT. Our patient had significant reductions in bleeding episodes and transfusion requirements following thalidomide therapy.

In summary, we successfully used thalidomide in the treatment of recurrent bleeding secondary to angiodysplasia in HHT, where hormonal and antifibrinolytic agents has not shown any benefit. Thalidomide is a low toxicity agent that acts as an inhibitor of vascular neogenesis and seems promising when other modalities of treatment have been unsuccessful.

Learning points

- Angiodysplasias are an important cause of anaemia and bleeding in HHT.
- Thalidomide seems to be promising drug in patients unable to benefit from other modalities of treatment.
- Consider thalidomide in refractory gastro-intestinal bleeding secondary to angiodysplasia.

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Competing interests None.

Patient consent Obtained.

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