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

Rendu-Osler disease: treatment with oestrogen/progestagen versus octreotide

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Summary

In Rendu-Osler disease, haemorrhages due to gastrointestinal vascular malformations are common. Surgical and endoscopic treatments for haemorrhage due to gastrointestinal vascular malformations are compromised when lesions are diffuse, escape identification or are inaccessible to treatment. Hormonal treatment with oestrogen and progestagens is still controversial based on contradictory results from two randomised clinical trials. Although somatostatin and its long-acting analogue, octreotide, have been reported to be beneficial in preventing rebleeding, there is no consensus on this type of treatment. This case report shows how the combination of ethinyloestradiol and norethisterone markedly reduced the need for blood transfusions with few side effects in one patient; in comparison, octreotide seems less effective but this could be related to a worsening of the disease.

BACKGROUND

Rendu-Osler disease has a prevalence of 1/5000 to 1/8000^{1–5} in the general population and is characterised by recurrent haemorrhage. Usual treatments comprise surgical and endoscopic procedures. Unfortunately, in some patients, surgical and endoscopic treatments for haemorrhage due to gastrointestinal vascular malformations fail when lesions are diffuse, escape identification or are inaccessible to treatment.⁶

A double-blind, placebo-controlled, cross-over trial of a daily dose of 0.05 mg ethinyloestradiol plus 1 mg norethisterone given by mouth in 10 patients with frequent and severe bleeding from gastrointestinal vascular malformations showed that this treatment is effective with no intolerable side effects.⁶ Other uncontrolled studies showed that oestrogen or oestrogen-progesterone treatment can effectively control recurrent epistaxis in patients with hereditary haemorrhagic telangiectasia (HHT).⁶

This case report illustrates and discusses the treatment options in a patient suffering from Rendu-Osler disease with recurrent haemorrhages that are not treatable by surgical or endoscopic procedures.

CASE PRESENTATION

In December 2003, a 68-year-old man with Rendu-Osler disease was referred to our outpatient clinic for evaluation and management of severe anaemia. He had suffered from Rendu-Osler disease since 1984 and had both epistaxis and chronic gastrointestinal tract bleeding. Other relevant medical problems were asymptomatic valvular aortic stenosis and alcoholic liver disease. After exclusion of coagulopathy, the patient was treated with blood transfusions several times a week, administration of ferrous sulphate and daily tranexamic acid. In 2004, repeated gastroscopy allowed argon-plasma coagulation of gastric, duodenal and jejunal telangiectases. Video

capsule endoscopy revealed multiple angiodysplasias in the small intestine. Colonoscopy showed two ceecal telangiectases without active bleeding. To maintain haemoglobin (Hb) values at or above 70 g/l, the patient required a mean of 2.2 blood transfusions weekly plus ferrous sulphate administration. Despite the blood transfusions, the patient's anaemia worsened. In January 2006, gastroscopy again allowed argon-plasma coagulation of telangiectases. An abdominal CT scan excluded an aortico-digestive fistula but showed multiple arteriovenous malformations (AVMs) in the pancreas, liver, spleen and, seemingly, in the ileum as well. Because the patient developed dyspnoea when his Hb level fell below 80–90 g/l, we used this value as an indication that a blood transfusion was needed. In 2006, the patient required a mean of 5.8 blood transfusions per week. After consultation with an endocrinologist and discussion with our ethics committee, and after explaining the potential adverse side effects and possible benefits of treatment to the patient, we started daily treatment with 50 µg ethinyloestradiol and 10 mg norethisterone in July 2006. After 1 month of treatment, the patient's need for blood transfusions began to decrease stabilising at a weekly mean of 2.4 blood transfusions. Because the patient complained of decreased libido and laboratory testing showed hypogonadism, sildenafil (50 mg) was prescribed. He reported no other side effects. As of July 2008, the patient remained clinically stable and still required about three red blood cell transfusions a week with continuing ethinyloestradiol/norethisterone treatment. At this time, the patient requested treatment with octreotide based on his sister's successful treatment with long-acting octreotide (Sandostatin LAR); the sister also has Rendu-Osler disease. Therefore, we switched our patient from oestrogen/progestagen to subcutaneous octreotide treatment. To evaluate tolerance, octreotide was initially administered once daily (day 1: 0.1 mg; day

Figure 1 Evolution of weekly blood transfusions. Oestrogen/progestagen treatment was started in July 2006 and ended in August 2008. Octreotide was started in August 2008 and ended in January 2009.

2: 0.1 mg; day 3: 0.15 mg; day 4: 0.15 mg; day 5: 0.2 mg). Once tolerance had been established, the patient received 10 mg octreotide once a month for 2 months, followed by 20 mg per month for 3 months. During the first 2 months of treatment with 10 mg octreotide, the patient required a mean of 4.7 red cell transfusions per week to attain a mean Hb level of 81 g/l. In the following 3 months, with 20 mg octreotide, he required 5.0 red blood cell transfusions per week to attain a mean Hb level of 80 g/l (figure 1). Despite this treatment, the patient's condition worsened; more and more blood transfusions were needed because of continued gastrointestinal bleeding. A Tc-99m pertechnetate scintigraphy with single photon emission CT was performed in 2009, which showed distal ileal bleeding. An arteriography showed a vascular malformation involving the inferior pancreaticoduodenal arteries. A first embolisation allowed a temporary improvement for 2–3 weeks but then, despite a second embolisation, the situation worsened. The patient developed heart failure probably because of the severe anaemia and his underlying aortic stenosis. He later died of sepsis due to translocation (related to gut flora).

DISCUSSION

HHT, or Rendu-Osler-Weber disease, is an autosomal dominant disorder associated with epistaxis, cutaneous telangiectasia and visceral AVMs. This disorder was first described by Henry Gawen Sutton in 1864 and was differentiated from haemophilia by Henri Jules Louis Marie Rendu in 1896. In 1901, William Osler described HHT as an inherited disorder; in 1907, Frederick Parkes Weber described a series of cases and in 1909 Hanes coined the

term 'HHT'.⁷ Mutations in endoglin, a receptor for transforming growth factor- β , have been found on chromosome 9 in some families with HHT, and linkage to chromosome 12q has been found in others⁸.

A HHT diagnosis is made according to the Curacao criteria: (1) spontaneous epistaxis, recurrent nose bleeds; (2) multiple telangiectases at characteristic sites (lips, oral cavity, fingers, nose); (3) visceral lesions, such as gastrointestinal telangiectasia, pulmonary AVM, hepatic AVM, cerebral AVM and spinal AVM; and (4) family history (a first degree relative with HHT). Diagnosis is confirmed by the manifestation of at least three of this criteria.^{7–9}

Gastrointestinal bleeding is a major cause of morbidity in patients with HHT¹⁰ and constitutes a therapeutic challenge. Surgical and endoscopic treatments for haemorrhage due to gastrointestinal vascular malformations are compromised when lesions are diffuse, escape identification or are inaccessible to treatment.⁶ The most common treatment for HHT is combination oestrogen and progestagen treatment.¹¹ Several case reports have suggested hormone treatment for controlling bleeding^{12–16} as have some uncontrolled trials^{17–19} and one small randomised clinical trial.⁶ In the latter study, 10 patients with frequent and severe bleeding from gastrointestinal vascular malformations were enrolled in a double-blind, placebo-controlled, crossover trial of a daily dose of oral ethinylloestradiol plus norethisterone. This treatment significantly decreased the need for transfusion. In 2001, a controlled trial of 72 patients randomised to receive placebo or ethinylloestradiol plus norethisterone for the prevention of rebleeding from gastrointestinal angiodysplasia concluded that oestrogen/progestagens treatment

was not useful for preventing rebleeding.²⁰ This study excluded both patients with cirrhosis and patients with HHT; in addition, the patients in the study had mild disease and the sample size was small. Only gastroduodenal angiodysplasia and colonic or diffuse angiodysplasia were considered. Small intestinal angiodysplasia alone was not considered, although Barkin demonstrated previously that obscure gastrointestinal bleeding due to distal small intestinal lesions responds to hormonal treatment.²¹ However, in the 2001 study,²⁰ the methodology used to localise bleeding was incomplete and the dosages of hormones were lower than dosages that have been demonstrated to be effective in both previous prospective studies and in randomised controlled trials.^{10 22 23} In a 2003 retrospective case series that included 43 patients with HHT, 16 patients received hormone treatment and 11 of them improved.¹⁰

The postulated mechanism of hormone treatment efficacy is induction of mucosal metaplasia by systemic oestrogens that results in thickening of the layers of keratinising squamous epithelium that protect against local trauma.^{6 24} Hormone treatment reduces gastric hyperaemia in animal models of portal hypertension or uraemia and shortens bleeding time in patients with chronic renal failure.²⁰

Concerning the adverse events, most are mild with metrorrhagia being the most common. Hormonal treatment was well tolerated in general. Oestrogen/progestagens did not appear to have a negative effect on the cardiovascular system.²⁰ The others potential side effects include nausea, loss of libido, testicular atrophy and gynaecomastia in men.

The alternative medical treatments for HHT include the weak androgen danazol, the use of which is supported by case reports and by prior use at Yale University Vascular Malformation Center, where a beneficial effect was seen in five men with HHT.^{10 25} Aminocaproic acid has also been described in case reports,¹⁰ progesterone has been used to treat a series of three patients²⁴ and octreotide has also been reported to reduce blood loss from intestinal angiodysplasia in case reports in a small uncontrolled study and in one case-control study.¹¹ In our patient, although octreotide seemed to be less effective than oestrogen/progestagens it is also possible that the disease itself was worsening.

It is important that there is further evaluation of oestrogen/progestagen treatment for treating patients with HHT despite the controversial study results. It may be an effective treatment (and perhaps the only effective treatment) for some patients. Our experience with this treatment is in

agreement with previous studies. In the single study²⁰ that failed to find a beneficial effect for oestrogen/progestagen treatment, the dosage of oestrogen was possibly too low to elicit a detectable therapeutic response. When prescribing this treatment for patients with HHT, it is important to use dosages that have been proven effective in the positive studies and case reports.

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Competing interests None.

Patient consent Obtained.

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Learning points

- In patients suffering from HHT, chronic bleeding is challenging when lesions are diffuse or inaccessible to endoscopic treatment.
- Although controversial, treating our patient with a combination of oestrogen/progestagen reduced rebleeding.
- This treatment may be considered in similar cases.

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