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SHORT REPORT

Norethisterone therapy for bleeding due to gastrointestinal telangiectases in Glanzmann's thrombasthenia

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Summary. We report a case of a patient with Glanzmann's thrombasthenia and anti-GPIIb/IIIa alloantibodies who developed life-threatening and intractable bleeding from gastrointestinal telangiectatic lesions. After a period of transfusion-dependent gastrointestinal bleeding despite tranexamic acid, oral iron, omeprazole and platelet transfusions, the use of oral norethisterone produced a significant improvement with a marked reduction in her transfusion requirements.

Keywords: Glanzmann's thrombasthenia, gastrointestinal telangiectases, norethisterone.

Glanzmann's thrombasthenia is a rare autosomal recessive platelet disorder due to deficiency of membrane glycoproteins IIb/IIIa. The clinical severity can vary, but in females mucocutaneous bleeding and menorrhagia are the primary clinical problems (George *et al*, 1990; Caen, 1989). Although platelet transfusions are useful when serious bleeding is present, in a small number of patients alloantibodies to glycoproteins IIb/IIIa develop, making patients refractory to the platelets of all donors.

CASE REPORT

The 27-year-old female was initially diagnosed as suffering from haemorrhagic disease of the newborn. She continued to bruise and bleed easily and the diagnosis of Glanzmann's thrombasthenia was made using standard platelet aggregation tests. During childhood she suffered recurrent oropharyngeal and traumatic skin bleeding, requiring long-term oral iron therapy.

At menarche, aged 14, she suffered significant menstrual bleeding with a fall in haemoglobin to 5·5 g/dl and was transfused 24 units of blood or blood products during a single hospital admission. Control was achieved only after random donor platelets had been administered, but following this transfusion she developed alloantibodies to glycoproteins IIb/IIIa. As a teenager she continued with severe uncontrolled menorrhagia (with haemoglobin levels falling to 4 g/dl), despite the use of the oral contraceptive pill and tranexamic acid. In view of this and as she had platelet alloantibodies, at the age of 22 she received 450 cGy pelvic irradiation in an attempt to achieve radiation menopause. Cyclical bleeding continued but the volume was significantly reduced and more manageable with regular oral contraceptive use.

At the age of 25 she presented with anaemia and a small number of gastric telangiectases were identified on endoscopy. Endoscopic laser photocoagulation therapy was attempted for all the visible telangiectatic areas. Over the subsequent 18 months her transfusion requirements increased and extensive telangiectases developed in the stomach and lower oesophagus. She did not have any skin telangiectases and no other family member was affected by a similar problem. Despite oral iron supplements, tranexamic acid and the oral contraceptive pill, Marvelon (desogestrel 150 μg, ethinyloestradiol 30 μg), she required almost weekly transfusions. A trial of HLA-matched platelets failed to shorten her bleeding time which remained > 20 min. A change of the oral contraceptive from Marvelon to Norimin (norethisterone 1 mg, ethinyloestradiol 35 μg) appeared to produce a slight reduction in the transfusion requirements. It was postulated that the norethisterone component was the agent responsible, so she was started on norethisterone 15 mg daily (the Norimin was discontinued). This resulted in a dramatic reduction in the transfusion requirements from 52 units of blood in the 100 d prior to the changeover to just 8 units in the subsequent 100 d (Fig 1). Two years later she remains on norethisterone and requires only infrequent transfusions.

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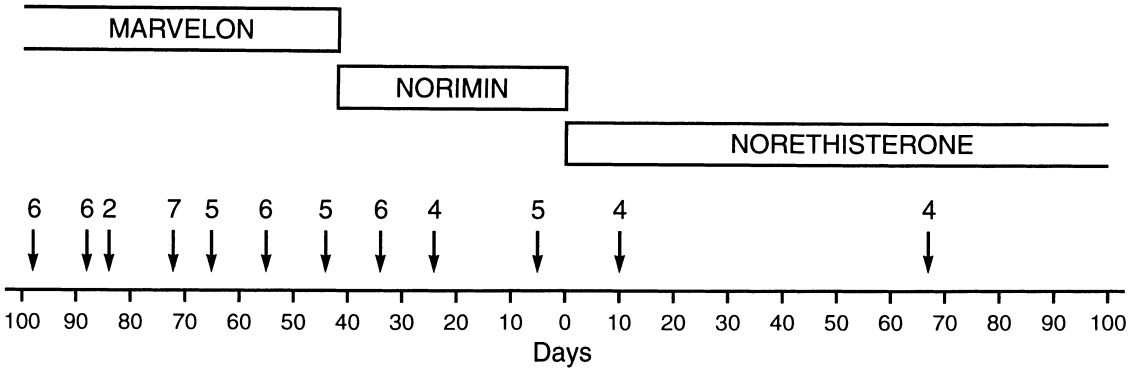

Fig 1. The number of units of blood transfused in the 100 d before and after starting single-agent norethisterone. Marvelon contains 150 μg desogestrel and 30 μg ethinyloestradiol, Norimin contains 1 mg norethisterone and 35 μg ethinyloestradiol, and norethisterone was given as a single dose of 15 mg daily.

DISCUSSION

Two aspects in this patients history are intriguing: why did she develop gastric telangiectases (angiodysplastic lesions) and why did treatment with norethisterone produce such a good response?

Telangiectatic lesions can occur in the gastrointestinal tract in patients suffering from hereditary haemorrhagic telangiectasiae (Osler Weber Rendu disease) (Vase, 1981; Van-Cutsem, 1993) and angiodysplastic lesions as a source of occult blood loss are increasingly recognized in the elderly (Boley *et al*, 1977). Our patient, who does not have hereditary haemorrhagic telangiectasiae, developed extensive gastrointestinal telangiectases in adult life and the reason for this is unknown. Interestingly, three similar cases of diffuse severe intestinal angiodysplasia have been reported in patients with Bernard-Soulier syndrome, another congenital platelet disorder due to a defect in platelet glycoproteins Ib/IX (Okamura *et al*, 1996). Angiodysplastic lesions and bleeding leading to iron deficiency have also been described in patients with type II von Willebrand's disease (Fressinaud & Meyer, 1993) and in patients with acquired von Willebrand's disease (Inbal *et al*, 1997). Furthermore, it has been suggested that in aortic stenosis where angiodysplastic lesions can occur, acquired von Willebrand's disease may be the link (Warkentin *et al*, 1992), since after aortic valve replacement both the angiodysplasia and the acquired bleeding disorder improved significantly (Lavabre *et al*, 1994).

Combined oestrogen–progesterone preparations have been use to treat gastrointestinal bleeding both in adult onset angiodysplasia (Moshkowitz *et al*, 1993) and in hereditary haemorrhagic telangiectases (HHT) (Van-Cutsem, 1993). In a double-blind placebo-controlled trial, van-Cutsem (1993) found that the use of oral 50 μg ethinyloestradiol plus 1 mg norethisterone reduced the transfusion requirements of patients with severe bleeding from gastrointestinal vascular malformations. However Vase (1981) found that oestrogen (4 mg oestradiol valerate daily) was unsuccessful in reducing the frequency or intensity of bleeding in HHT. In our patient the use of low-dose norethisterone with oestrogens appeared to provide a small benefit but did not significantly reduce her transfusion requirements. We therefore went on to use 15 mg of norethisterone daily without oestrogens and found that this was superior in reducing bleeding. We are not aware of any other report in which a single-agent progestogen such as high-dose norethisterone was used to reduce angiodysplastic bleeding.

It is not known how hormonal therapy is able to reduce angiodysplastic bleeding, but it has been suggested that it may be due to a modulation of mucosal blood flow. In a rat animal model of angiodysplasia, Panes *et al* (1994) were able to show that oestrogen–progestagen therapy induced a significant reduction in gastric mucosal blood flow, and also reduced the density and relative surface area of mucosal vessels.

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