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

Long-time octreotide in an adolescent with severe haemorrhagic gastrointestinal vascular malformation

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Summary

Gastrointestinal vascular malformations are a rare cause of acute or chronic blood loss. Usually they are treated by endoscopic obliteration or surgical resection. When such a therapy is inapplicable, pharmacotherapy may be required. At the age of 15 years, our female patient suffered from transfusion dependent recurrent gastrointestinal haemorrhage due to multiple gastrointestinal vascular malformations. Gastroscopy, colonoscopy and capsule endoscopy revealed numerous foci making both endoscopic obliteration and complete surgical resection impossible. Neither regular transfusions nor substitution with coagulation factors were helpful. However, subcutaneous octreotide resulted in immediate stop of bleeding. Initial treatment by daily subcutaneous injections was followed by monthly depot application. Over 3 years only 2 transfusions had to be given. The patient required thyroxin substitution, otherwise, no side effects occurred and the girl had a good quality of life. The authors conclude that octreotide is safe and effective in gastrointestinal angiodysplasias inaccessible to endoscopy or surgery.

BACKGROUND

While haemangiomas consist of proliferating tissue growing transiently in infants and usually undergo spontaneous involution, vascular malformations are present from birth and grow just in concert with the rest of the body.¹ Vascular malformations may have arterial, venous, capillary or lymphangios origin, they may be a single site or a multilocal disease, and they may involve any organ in the body.² Both localised or multiple vascular malformations may be sporadic, or part of a more complex syndrome: in the blue rubber bleb nevus syndrome, multiple cutaneous venous malformations with a distinctive blue colour and rubbery consistence are associated with gastrointestinal malformations; in Klippel–Trénaunay syndrome, subcutaneous arteriovenous malformations are spread all over an extremity leading to local hypertrophy; in Proteus syndrome, this is associated with irregular benign tumour formation.³ Histologically, haemangiomas and vascular malformations are composed of multiple vascular channels lined with a single layer of dysplastic endothelium, supported by a fibrous connective tissue scaffold.³

The need for therapeutic interventions in vascular malformations depend on the clinical problems caused by the disorder: while cutaneous malformations usually lead to cosmetic or functional problems, gastrointestinal disorders often manifest themselves by chronic or acute blood loss. This occasionally leads to transfusion dependency, and may even be life threatening.^{4,5} While haemangiomas might be a target of pharmacological therapies like steroids, interferon, some other antiangiogenetic substances, or, as recently described, β -sympatholytic agents,⁶ these drugs usually are ineffective in vascular malformations. Common therapeutic approaches of gastrointestinal vascular malformations include endoscopic obliteration by

laser, or surgical resection of the involved gut portion.^{1,7} However, in cases in which such a therapy is not applicable, for example due to the extent or distribution of the malformation, pharmacological approaches may be urgently required.⁷

Here, we report on a girl with multiple vascular malformations all over the body since early childhood who, at the age of 15 years, suffered from progressive gastrointestinal haemorrhage requiring frequent blood transfusions. Both endoscopic obliteration and complete surgical resection were impossible. Application of subcutaneous octreotide, however, resulted in immediate halt of the bleeding.

CASE PRESENTATION

We report on a girl who after uneventful previous and family history first presented at the age of 4 years 3 months with a soft, slightly painful tumour in the left distal forearm. Imaging by Doppler sonography and MRI indicated a vascular malformation. The tumour was resected. Histology showed a conglomerate of large vessels, mostly venous, with proliferations of connecting tissue and some muscular and osseous structures, indicating a benign arteriovenous angiodysplastic malformation with reactive periostitis.

Whole body imaging with ultrasound and MRI revealed numerous vascular malformations all over the body, for example, a nodule of about 5 cm diameter in the right axilla, several paravertebral formations including one in the neck of 3 cm and two in the back musculature, of about 6 cm; several smaller tumours at the chin, the orbita, the nasopharynx and the tongue, some small nodules in both arms and legs, up to 3 cm in diameter. In addition, a formation was found in the posterior mediastinum, measuring 3 x 6 cm. Several tumours were

Figure 1 (a-c) Abdominal MRI (T2-weighted) showing multiple vascular malformations in gut, spleen, mediastinum and paravertebral area. Composed whole body MR imaging T2-weighted turbo-inversion recovery-magnitude (TIRM) inversion recovery) showing multiple hyperintense cystic lesions, mostly lobulated, in cutis, subcutis, bones, paravertebral, in parenchymal organs and gut.

within the liver and the spleen, partially with calcifications, measuring up to 3 cm. Imaging was typical for a vascular malformation (figure 1). Gastroscopy, colonoscopy and capsule endoscopy showed two small manifestations in the stomach, diffuse submucosal vascular malformations extending throughout nearly the complete proximal jejunum, and, in the terminal ileum, several polypous vascular formations; besides, two large polypous malformations in the distal colon mucosa were found (figure 2a,b). The malformations did not have the typical bluish colour or consistence of blue rubber bleb lesions, although otherwise, the presentation was similar to blue rubber bleb syndrome. The patient had no signs of hemihypertrophy or of non-vascular tumours and she had normal cardiac function. Brain MRI was normal. A multi-organ vascular malformation syndrome was diagnosed.

While initially, only a mild iron deficient anaemia was found that was treated by substitution, from the age of

9 years on the patient suffered from continuous gastrointestinal blood loss leading to severe anaemia that required repetitive transfusions.

Several therapeutic approaches were discussed and undertaken in our patient. Operative resection was applicable only on some lesions at the extremities and in the axilla where they had caused pain or functional impairment. Resection of asymptomatic paravertebral lesions appeared unnecessary. Some smaller lesions in the skin and stomach could be obliterated by laser. Since blood supply of the malformations originated from several different arterial vessels, embolisation of the mediastinal or abdominal foci appeared inapplicable or too risky. An experimental therapy with interferon- α , given as subcutaneous injection, was ineffective.

At the age of 15 years, gastrointestinal haemorrhage became progredient, leading to recurrent critical anemia even 2 or 3 days after blood transfusions. Transfusions

Figure 2 Endoscopic images of the gut (a) planar arteriovenous malformation in the jejunum area (image generated by capsule endoscopy), (b) blue-rubber-bleb-like arteriovenous vessel formation in the colon.

were required more than once weekly. Several times, the patient received activated factor VII concentrates; continuously, substitution with a von-Willebrand-factor-containing factor VIII preparation and a factor XIII concentrate were performed.

TREATMENT

Since none of these approaches led to consistent improvement of the condition, an experimental treatment with octreotide was initiated with fully informed consent of both parents and patient.

Starting at the age of 16 years 11 months, the patient received octreotide (SandostatinTM 100 µg twice daily subcutaneously; patient's weight 67 kg). Within several days, the bleeding stopped. Thereafter, treatment was changed to somatostatin 1 × 100 µg s.c. daily, and later, monthly 60 mg lanreotide acetate (Somatuline AutogelTM) treatment as a depot preparation.

OUTCOME AND FOLLOW-UP

The treatment was well tolerated. However, the patient developed secondary hypothyroidism requiring L-thyroxine substitution. In addition, transient amenorrhea and weight gain were noted. The latter could be controlled by dietary advice.

During a follow-up period of 2 ½ years, only two erythrocyte transfusions were required.

Otherwise, the girl still has no side effects and a good quality of life. Since unfortunately there was no consent for a follow-up endoscopy, we do not know whether there occurred any morphological change in the gastrointestinal tract upon treatment.

DISCUSSION

The peptide hormone somatostatin originally was found to inhibit secretion of growth hormone in the pituitary gland, leading to its name; however, it has numerous functions throughout the body, especially within the gastrointestinal tract, but also in the central nervous, immune and endocrine system.⁸ Particularly, somatostatin and its synthetic analogue, octreotide, influence the effects of gastrin, vasoactive intestinal polypeptide, and other gastrointestinal peptides, which leads to a marked decrease of

splanchnic blood flow, intestinal motility and gastric emptying.⁸ Therefore, from the early seventies, somatostatin or octreotide have been applied as an emergency medication for acute esophageal varice bleeding by reduction of portal venous pressure.⁹

Pharmacological treatment of gastrointestinal haemorrhage caused by vascular malformation, going along with normal splanchnic blood pressure, appears particularly difficult. Numerous therapies like corticosteroids, cyclophosphamide, interferon, tranexamic acid, vasopressin, or others¹⁰ have been without proven benefit. In a randomised study, the application of estrogen/progesterone preparations, was shown to be ineffective.¹¹ Only coagulation factor supplementation may have some benefit.¹⁰ The feasibility of octreotide treatment, however, was shown in numerous studies, mostly in adults^{5 12–14} including one randomised study,¹¹ which were recently reviewed in a meta-analysis.¹⁵ Patients with bleeding gastrointestinal vascular malformations responded significantly to treatment with octreotide.¹⁵ Nardone *et al.* described 17 patients with chronic gastrointestinal bleeding, including numerous vascular malformations, who received octreotide 0.1 mg subcutaneously twice daily for 6 months.¹³ While in some, haemoglobin became stable during the follow-up, in others, overt rebleeding or anaemia followed after cessation of treatment.¹³

In a randomised study, Junquera *et al.*¹¹ treated 32 patients with gastrointestinal angiodysplasia with or without octreotide 50 µg s.c. twice daily, observing 23% versus 48% treatment failure.

The mechanism of octreotide in bleeding gastrointestinal vascular malformation is not entirely clear. Besides its effects on splanchnic blood flow, somatostatin analogues may also have a direct antiangiogenic effect through a block of growth-factor-stimulated mitogen-activated protein kinase and endothelial nitric oxide synthase activities.^{13 16}

Side effects of octreotide that are particularly relevant in long-term treatment, include diarrhoea, delayed gastric emptying, ileus, or abdominal pain, further cholelithiasis, both hypoglycemia and hyperglycemia and sinus bradycardia.^{8 14 15} Nausea, pain at the injection site, elevation of liver enzymes, chest pain, emesis, headache, dizziness, fatigue and flushing have rarely been reported during

octreotide treatment.⁸ Inhibition of thyreotropin may also result in hypothyroidism.⁸

Chronic treatment of children and teenagers may be regarded as a particular problem because of endocrinological side effects. No larger series but numerous case reports have been published so far.^{17 18} In paediatric liver disease with portal hypertension leading to acute haemorrhage, however, octreotide treatment was shown to be safe and effective.^{8 19} In infants, adrenal suppression and growth retardation were described, but followed by catch-up growth.⁸

In our patient, the treatment appears quite effective and safe. Hypothyroidism could be treated by substitution. Whether the weight gain the patient observed and which could be controlled by diet was really a consequence of octreotide treatment, remains open. We conclude that octreotide is a safe and effective treatment option in gastrointestinal vascular malformations inaccessible to endoscopy or surgery.

Learning points

- ▶ Vascular malformations have to be carefully separated from haemangiomas.
- ▶ Octreotide is very effective in gastrointestinal vascular malformations inaccessible to endoscopy or surgery.
- ▶ Long-term treatment is possible without severe side effects besides smaller endocrinological abnormalities.

Competing interests None.

Patient consent Obtained.

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