Two for the price of one: a dual treatment benefit of long-acting octreotide in occult bleeding and diuretic intractable ascites

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Abstract

Transfusion-dependent anaemia and portal hypertension are recognised complications of hereditary haemorrhagic telangiectasia (HHT). The anaemia is a result of chronic bleeding from gastrointestinal telangiectasias, which are usually multiple and located throughout the gastrointestinal tract. As a result, treatment with argon plasma coagulation via gastroscopy and or colonoscopy is often insufficient to prevent ongoing blood loss. Portal hypertension in HHT occurs as a result of blood shunting between the hepatic artery and the portal vein within the liver. The somatostatin analogue octreotide has been used as a treatment for bleeding angiodysplasia; however, its possible role as a treatment for diuretic intractable ascites secondary to portal hypertension has not been previously established. The authors report a case that apparently illustrates a dual benefit of long-acting octreotide in the management of both occult bleeding and refractory ascites in a patient with HHT.

Case report

An 86-year-old man presented in March 2009 with breathlessness and a haemoglobin (Hb) count of 6.4 g/dl (mean cell volume 91 fl). There was no history of haematemesis or melaena. He was diagnosed with hereditary haemorrhagic telangiectasia (HHT) 40 years ago and also had hypertension and type II diabetes mellitus. On admission, he was taking amlodipine, metformin and ramipril but no antiplatelet agent. He did not drink alcohol to excess. Physical examination was unremarkable apart from buccal telangiectasia. His liver function tests were mildly deranged (alanine transaminase 18 IU/litre, alkaline phosphatase 519 IU/litre, bilirubin 15 mmol/litre); in

addition, he had mildly impaired clotting (prothrombin time 15.9 seconds) and a low albumin of 23 g/litre. An upper gastrointestinal endoscopy showed multiple actively bleeding telangiectasias in the gastric antrum, which were injected with epinephrine. He then had repeat endoscopies at monthly intervals over the following 5 months. On each occasion, he received argon plasma coagulation treatment directed at the gastric telangiectasias, which became progressively smaller in size and number; by the sixth endoscopy, there was just a single, small, non-bleeding lesion (figure 1), but on this occasion, grade 1 oesophageal varices without any stigmata of recent haemorrhage were also noted.

Despite eradication of the gastric telangiectasia and continuous oral iron therapy, he still required two units of blood transfusion every 3–4 weeks in order to maintain a Hb count of 9 g/dl. We did not pursue colonoscopy or capsule endoscopy because we felt the patient was unfit for further invasive investigation. A CT pneumocolon was performed (figure 2), which excluded large bowel malignancy but did show evidence of portal hypertension with a small cirrhotic liver containing multiple telangiectasias. Three months following the initial presentation, he developed ascites and bilateral leg oedema. A diagnostic ascitic tap showed a transudate sample with normal cell counts and negative cytology. Blood tests showed normal ferritin, caeruloplasmin and α 1 anti-trypsin levels, negative hepatitis B and C serology and a negative autoimmune screen. An echocardiogram reported reasonable left and right ventricular functions.

Figure 1 Endoscopic image of single, non-bleeding gastric telangiectasia situated in the proximal body of the stomach on retroflexion following repeated argon plasma coagulation treatment.

He was started on a combination of furosemide and spironolactone for the ascites and carvedilol as primary prophylaxis for the oesophageal varices. Despite this, his ascites became intractable with associated renal failure. As a result, the diuretics and metformin were stopped and he received intravenous Glypressin and albumin to stabilise his renal function. Subsequently, he had a total-volume paracentesis with albumin cover. Further attempts to restart diuretics were associated with worsening renal impairment; therefore, his ascites was managed with paracentesis, which was required twice within the next fortnight. His transfusion requirements over the next 2 months doubled to a total of eight units. As he did not have any melaena and was frail, we decided not to undertake any further gastroscopies. In December 2009, he was started on long-acting octreotide, given intramuscularly at a dosage of 20 mg per month. He required a two-unit transfusion the next month but subsequently was able to maintain a Hb count of 9 g/dl without receiving any more blood. His paracentesis requirement was also reduced from three sessions in 5 weeks to once a month. He was maintained on a minimal dose of diuretics (spironolactone 25 mg once daily) and his renal function remained stable. Overall, his quality of life improved with fewer visits to hospital.

Discussion

Octreotide is a somatostatin analogue, which is an established treatment for acute variceal bleeding.¹ Given as a continuous infusion, it promotes haemostasis and reduces the rate of rebleeding after endoscopic therapy.¹ Its primary mode of action is thought to be mediated through the inhibition of vasodilator peptides, which results in a decreased portal pressure by reducing the blood flow.² It has also been recognised that octreotide has an inhibitory effect on vascular endothelial growth factor—this could be beneficial in controlling occult bleeding from vascular

Figure 2 Contrast CT in the venous phase showing hepatic vascular malformation, irregular liver surface, dilated portal vein and ascites.

malformations in the digestive tract.^{2,3} Indeed, several small studies have used this agent in the treatment of gastrointestinal bleeding due to angiodysplasia.^{2,4-6} A more recent study of 32 patients concluded that octreotide, given as a twice-daily subcutaneous regime, was more beneficial than a placebo injection in reducing the recurrence of bleeding from angiodysplasia.⁷

Long-acting preparations of octreotide have been formulated to treat conditions such as acromegaly. The efficacy of this preparation to reduce bleeding from intestinal angiodysplasia has been reported in several case reports^{3,8} and a small case series.⁹ In this study, all patients were assessed after a year's treatment and were shown to have significantly fewer and smaller lesions at endoscopy.⁹ There was a corresponding reduction in transfusion requirements and hospital stay. The authors felt that a long-acting preparation was more convenient to administer and also avoided fluctuating blood levels of the drug.⁹ The optimal dosage for this indication is unclear; they found no difference between 10 and 20 mg dosages given intramuscularly each month.⁹ The potential adverse effects of the treatment are diarrhoea and hyperglycaemia, although the treatment has been reported as well tolerated in most studies.

In our patient, the ongoing blood loss after the eradication of the gastric telangiectasias is likely to be due to other sites of bleeding in either the small or the large bowel. Up to 80% of patients with HHT have gastric and small bowel telangiectasia although only one-third of them have symptomatic bleeding, usually presenting in the fifth or sixth decade of life.¹⁰ The international guidelines for the management of these lesions recommend supportive treatment with oral or intravenous iron.¹⁰ Endoscopic treatment

using argon plasma coagulation can be of use but is seldom totally effective as the vascular malformations tend to reoccur after local treatment and are usually in multiple disseminated sites that are relatively inaccessible such as the small bowel.¹¹ The previously reported benefit of oestrogen/progesterone hormonal treatment is not clear as a recent trial had shown no significant reduction in the incidence of rebleeding from angiodysplasia.¹² The decrease in blood transfusion requirements in our patient after starting treatment with long-acting octreotide apparently reflects its efficacy in controlling the occult blood loss from gastrointestinal telangiectasias.

Our patient was shown to have developed portal hypertension. Hepatic vascular malformations are common in HHT and have been described in 84% of cases.¹³ They are mainly asymptomatic but can present with portal hypertension due to the shunting of blood from the hepatic artery to the portal vein.¹⁴ True liver cirrhosis is rare and is usually related to the presence of cofactors or portosystemic shunting.¹⁴ CT scans with contrast often show areas of abnormal parenchymal perfusion, telangiectasias and large confluent masses; Doppler ultrasound may reveal a distended hepatic artery.¹⁴ It is possible to treat these vascular malformations by arterial embolisation; this technique has been used if there is coexisting high output cardiac failure.¹⁵ A recent case report has suggested a benefit in using the vascular endothelial growth factor antibody bevacizumab to reverse the effects of portal hypertension secondary to vascular shunting in HHT.¹⁶ However its use is limited by side effects such as mucosal bleeding due to epistaxis.¹¹ Other antiangiogenic agents such as thalidomide have also been shown to reduce the number and size of angiodysplastic lesions; however, thalidomide can be a potent sedating agent, which might render it unsuitable especially for older patients.^{17, 18} We performed a literature search but could not find any previous report describing the use of long-acting octreotide for the management of portal hypertension in patients with HHT. However, its potential benefit in managing chronic portal hypertension in cirrhotic patients has been suggested after it was shown that there was a significant reduction in the hepatic venous portal gradient after 3 months of treatment using long-acting octreotide at a dose of 20 mg.¹⁹ As the CT scan in this case showed a small irregular liver, we propose that it is likely the portal hypertension in our patient is due to a combination of true liver cirrhosis secondary to non-alcoholic steatohepatitis and hepatic artery–portal vein shunting as a result of hepatic vascular malformations.

Our patient subsequently developed diuretic intractable ascites. The British Society of Gastroenterology guidelines suggest considering a transjugular intrahepatic portosystemic shunt (TIPS) in patients who require frequent paracenteses.²⁰ In our patient, due to comorbidities and general fragility, neither arterial embolisation nor TIPS was considered an appropriate

option. We therefore considered octreotide as a potential treatment option and apparently showed a dual benefit in reducing portal hypertension and occult bleeding from the HHT lesions. We chose a long-acting preparation for the convenience of the patient. In the 6 months following the initiation of treatment, his transfusion and therapeutic paracentesis requirements dropped significantly.

Conclusion

Our patient had required a total of 43 units of blood transfusion within a 7-month period with one prolonged hospital stay to stabilise his diuretic intractable ascites. Since starting the long-acting octreotide treatment, he needed only four units of blood transfusion over 5 months. His paracentesis requirement also reduced from once every 10 days to once every 6 weeks. He has been able to resume most of his daily activities due to improved energy levels and has avoided further hospital admissions. The treatment has been well tolerated and his glycaemic control has remained stable. This case confirms the role of long-acting octreotide in occult bleeding from intestinal telangiectasias and, for the first time, suggests it may have a potential benefit in treating diuretic intractable ascites in patients who are unsuitable for liver transplant or TIPS.

Competing interests None.

Patient consent Obtained.

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