

CASE REPORT

Nintedanib as a novel treatment option in hereditary haemorrhagic telangiectasia

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SUMMARY

A 70-year-old patient with known hereditary haemorrhagic telangiectasia (HHT) was seen regularly in our outpatient clinic. He underwent multiple therapeutical interventions, including both surgical and medical, for the treatment of recurrent epistaxis without sustained success. Due to a concurrent diagnosis of idiopathic pulmonary fibrosis, treatment with the tyrosine kinase inhibitor nintedanib was initiated, after which point the patient reported a dramatic and unanticipated improvement in his epistaxis and skin telangiectasia. On the basis of this case report, we propose that nintedanib may be a potential treatment option for refractory epistaxis in HHT.

BACKGROUND

Hereditary haemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare autosomal -dominant genetic disorder characterised by mucocutaneous telangiectasias and organ arteriovenous malformation.¹ Nasal telangiectasias are common and seen in 90% of HHT cases, resulting in frequent and difficult-to-treat spontaneous epistaxis.¹ The Epistaxis Severity Score (ESS) is used for the objective evaluation of epistaxis severity.¹ Although there are multiple therapeutical options available for epistaxis in HHT, outcomes of treatment are highly unpredictable and must be tailored to each patient. Surgical treatment options include coagulation with laser or electrocoagulation, submucosal radiofrequency, septodermoplasty, embolisation and the Young's procedure as a last resort, which involves the unilateral or bilateral surgical closure of the vestibulum.² Medical therapeutical options include systemic and topical oestrogen, partial antioestrogens such as tamoxifen, thalidomide, beta-blockers, acetylcysteine and tranexamic acid.² In recent years, monoclonal antibodies directed against vascular endothelial growth factor (VEGF) have emerged as one possible treatment modality, among which bevacizumab has shown promising benefit.² This report summarises the currently available medical options for epistaxis treatment in HHT and describes nintedanib as a possible novel therapy.

CASE PRESENTATION

A 70-year-old male patient suffered from frequent and difficult- to-treat epistaxis since the age of 16 years. Both his mother and grandmother died secondary to heart failure related to significant

epistaxis and subsequent severe anaemia. The patient was diagnosed with HHT and genetic testing confirmed the presence of a heterozygous pathological mutation c.1232G>A (p.Arg411Gln) in the *ACVRL1* (*ALK1*) gene. For the management of frequent epistaxis, treatment with laser coagulations and interventional angiography with embolisation were carried out between 1988 and 1996, but without sustained success. Although tranexamic acid and oral anthocyanins were also used, the patient's epistaxis continued on a once weekly basis and resulted in decreased quality of life. The patient had several telangiectasias of the face, mouth, décolleté and palms, which were removed using repeated laser therapy and by surgical resection. He was also noted to have urinary bladder telangiectasia on cystoscopy following evaluation for macroscopic haematuria.

In 2015, the patient reported a significant decrease in his general quality of life and subsequent investigations revealed a diagnosis of idiopathic pulmonary fibrosis (IPF). Pulmonary hypertension, which is a rare manifestation of HHT and mainly seen in patients with *ALK1* mutations,³ was also confirmed and thought most likely to be HHT related. A right-heart catheterisation raised suspicion for the presence of a pulmonary arteriovenous malformation, but this was not seen on CT of the chest. An abdominal ultrasound showed irregular liver parenchyma and a conspicuous Doppler pattern suggestive of a presumed shunt.

TREATMENT

Following the diagnosis of IPF, treatment with the tyrosine kinase inhibitor nintedanib was started at an oral dose of 150 mg two times a day, with the intent of preventing further progression of the pulmonary fibrosis.

OUTCOME AND FOLLOW-UP

Subsequent to initiating nintedanib, the patient's pulmonary function tests stabilised and no further disease progression was seen on CT. He tolerated nintedanib therapy without any considerable side effects, including significant weight loss or gastrointestinal disturbances. Haemoglobin levels were measured as normal prior to and after starting nintedanib, and there was no evidence of thrombocyte dysfunction on haematological investigations. There was a subjective improvement in physical performance, as reported by patient, and an unanticipated improvement in epistaxis after 3 weeks of



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nintedanib treatment. While the patient had previously experienced several episodes of epistaxis per day of 6 to 15 min duration, this decreased to only one episode per month of <1 min, even with blowing of his nose. Objectively, his ESS decreased from a moderate score of 5.53 to a mild value of 0.51.¹ This improvement has been sustained while on nintedanib and there has been no worsening of his epistaxis in the last 12 months of follow-up. Furthermore, the telangiectasias described above have also disappeared in some areas, especially over the auricles.

DISCUSSION

HHT is an autosomal-dominant disorder affecting multiple organ systems. With an estimated prevalence of 1:10 000–15 000, it qualifies as an orphan disease.^{1,2} A diagnosis of HHT may be made on clinical grounds, based on the Curaço criteria published in 2000, or if genetic testing shows a pathological mutation in one of the known HHT gene, including *ALK-1*, *ENG* and *SMAD-4*.

Recurrent epistaxis is the most common symptom of the disease and has very important implications on the quality of life of patients.¹ Although numerous treatment modalities exist for epistaxis, most offer only temporary relief in HHT. In severe cases, systemic therapy should be strongly considered and may provide a more sustained benefit. While hormonal therapy with oestrogen and antioestrogens can be successfully applied for the treatment of epistaxis, systemic side effects including the increased risk of malignancy are not negligible.² Through an antiangiogenic pathway, thalidomide reduces the incidence of anaemia and epistaxis in HHT, but potential side effects including neuropathy and teratogenicity are once again serious.² The efficacy of tranexamic acid and *N*-acetylcysteine on epistaxis are also well described, but do not improve any of the other HHT features.² While non-selective beta-blockers also have an antiangiogenic effect, comprehensive studies in HHT are still lacking.² Bevacizumab is a direct VEGF inhibitor⁴ and has been shown in multiple small series studies to have a positive impact on iron-deficiency anaemia, epistaxis and other systemic symptoms in HHT.^{4,5} However, once again, the potential side effects of bevacizumab should not be understated and include thromboembolic events, nasal septal perforation, gastrointestinal perforations and arterial hypertension.^{2,4}

The case presented here supports the hypothesis that systemic therapies using novel monoclonal antibodies against the VEGF pathway may prove very promising in the treatment of epistaxis and other manifestations of HHT. The tyrosine kinase inhibitor nintedanib inhibits several receptors, including VEGF, by blocking fibroblasts, which are critical players in the pathophysiological mechanism of IPF.⁶ VEGF also plays a key role in the regulation of neovascularisation. VEGF plasma concentrations and transforming growth factor- β (TGF- β) levels are known to be higher in HHT, with TGF- β stimulating the production of VEGF.⁵ As a tyrosine kinase inhibitor, we hypothesise that nintedanib, therefore, acts through antiangiogenesis by indirect inhibition of the VEGF receptor.

In a case report from 2010, a patient with HHT was treated with infliximab, a tumour necrosis factor (TNF)- α antibody, for the management of Crohn's disease. The patient showed a dramatic improvement in epistaxis and anaemia, which may be attributed to the indirect effect of TNF- α antibodies on vascular endothelial cells.⁷ In 2013, a different case report was published on a patient with *SMAD4*-related juvenile polyposis HHT syndrome.⁸ The patient received dasatinib, a multikinase inhibitor, for the treatment of Philadelphia-positive acute lymphoblastic leukaemia. Following the initiation of dasatinib,

the patient experienced multiple episodes of gastrointestinal haemorrhage which, in combination with myelosuppression and thrombocytopenia, resulted in severe anaemia and death.⁸ Thrombocytopenia and myelosuppression have not, however, been described as side effects of nintedanib.⁶ In our patient, there was no evidence of thrombocyte dysfunction and the patient has not experienced any serious side effects related to nintedanib, including liver dysfunction, arterial thromboembolic events, bleeding, emesis, abdominal pain, severe diarrhoea or hypertension.⁶ Given the successful and sustained improvement in epistaxis and telangiectasia in our patient, nintedanib should be considered as a potential therapeutic option in HHT. Further larger cohort studies are needed to determine the safety and efficacy of nintedanib in the treatment of HHT.

Learning points

- ▶ Hereditary haemorrhagic telangiectasia (HHT) is an inherited multisystem disease with spontaneous epistaxis as the most common manifestation.
- ▶ Therapeutic options in patients with HHT should target systemic manifestations.
- ▶ In this case report, we show that nintedanib may be a potential therapeutic option for the treatment of epistaxis and other disease-related manifestations in HHT.
- ▶ The patient described here had no significant side effects and continues to have sustained relief of epistaxis since starting nintedanib over 12 months ago.
- ▶ Further studies are needed to evaluate the use of nintedanib as a novel treatment option in HHT.

Contributors EK-S: writing the manuscript, looking for the necessary data about the patient and in the literature. DH: correcting the manuscript mainly regarding the nose symptoms and therapy of the disease; physician of the patient because of the nose bleed. TS: correcting the manuscript mainly regarding to the pulmonary symptoms of the disease. Physician of the patient because of the idiopathic pulmonary fibrosis. MBS: supervisor of the whole manuscript, further correcting, advising.

Competing interests None declared.

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