

Case Report

Hereditary Hemorrhagic Telangiectasia/ Avastin

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This is the first scientific report of hereditary hemorrhagic telangiectasia (HHT) epistaxis treatment by intranasal spraying of the vascular endothelial growth factor (VEGF) inhibitor bevacizumab (Avastin). Epistaxis in patients with HHT is a morbid, mortal condition that is difficult and unpleasant to manage. Nasal telangiectasia growth is modulated by VEGF, which is elevated in HHT patients. Bevacizumab is a VEGF inhibitor that diminishes epistaxis when administered intravenously or injected locally, or as reported here when sprayed topically onto the nasal mucosa.

Key Words: Hereditary hemorrhagic telangiectasia, epistaxis, endothelial growth factors, vascular endothelial growth factors, vascular endothelial growth factor inhibitors, bevacizumab, Avastin.

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INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) epistaxis is a difficult and messy problem for patients. The bleeding is unpredictable. They have to be constantly ready to leave whatever they are doing and attend to their bleeding, and when they cannot control the epistaxis they have to go to the emergency department to get cauterized and have their nose packed. A majority of patients are anemic. Oral iron is of little value, so many are on intravenous (IV) iron. Most have had several operations and multiple blood transfusions, and most are deathly fearful of someone permanently suturing their nose closed. Physicians have little to offer, and so

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these patients are tough. Surgical outcomes are generally poor. A medical therapy such as a vascular endothelial growth factor (VEGF) inhibitor spray would be welcome by both patient and doctor.

CASE REPORT

A 45-year-old male presented with a chief complaint of frequent episodes of epistaxis. His past medical history was significant for HHT. Other manifestations of HHT included elevated liver enzymes secondary to multiple hepatic arteriovenous malformations (AVMs), which were otherwise asymptomatic, and a small pulmonary AVM discovered during routine screening. He was being treated for iron deficiency anemia with oral ferrous sulfate. He took no other medications, had no medical allergies, and was otherwise healthy.

His epistaxis began prior to 10 years of age, and he had undergone several nasal cauterizations using silver nitrate during his second and third decades of life. His epistaxis occurred at least once on most days and multiple times a day several times a week. His anemia had been diagnosed 2 years earlier when his hemoglobin was found to be 8.2 gm/dL. With the use of supplemental iron his hemoglobin levels varied between 11 and 14 gm/dL.

Because of the frequent epistaxis and varying hemoglobin levels, he sought treatment at the University of California, San Diego nasal dysfunction clinic. After discussing treatment with laser and submucosal bevacizumab, he asked if the bevacizumab could be injected without the anesthesia and the lasering. After local anesthesia with 0.25% Pontocaine spray, 100 mg of bevacizumab was injected submucosally into both anterior nasal cavities without injection into the cartilaginous septum. The patient had no difficulties and within a week all nasal bleeding stopped. The patient experienced virtually no bleeding for the ensuing 4 months and during this time successfully climbed Mount Kilimanjaro. However, at the end of 4 months his bleeding resumed, albeit less severely.

We discussed the idea of applying the bevacizumab topically. We agreed to do this and began treating around April 1, 2009. A total of 50 mg of bevacizumab

The purpose of these questions is to calculate a severity score of epistaxis (nose bleeding) for patients with Hereditary Hemorrhagic Telangiectasia. Treatment for epistaxis should be determined by a care provider with experience in treating patients with HHT, and this calculation should serve as an adjunct to clinical evaluation. For more information regarding the meaning of this score, please discuss with your health care provider. Please answer each of the following questions as they pertain to your TYPICAL symptoms since your last treatment for nose bleeding. Please answer all questions.

1. How often do TYPICALLY have nose bleeding?

- Less than monthly
- Once per month
- Once per week
- Several per week
- Once per day
- Several per day

2. How long do your TYPICAL nose bleeding episodes last?

- < 1 minute
- 1-5 minutes
- 6-15 minutes
- 16-30 minutes
- > 30 minutes

3. How would you describe your TYPICAL nose bleeding intensity?

- Not Typically Gushing or Pouring
- Typically Gushing or Pouring

4. Have you sought medical attention for your nose bleeding?

- No
- Yes

5. Are you anemic (low blood counts) currently?

- No
- Yes

6. Have you received a red blood cell transfusion SPECIFICALLY for nose bleeding?

- No
- Yes



Raw Epistaxis Severity Score Normalized Epistaxis Severity Score

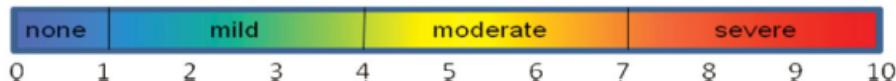


Fig. 1. HHT Foundation Epistaxis Severity Scoring (ESS) Tool for hereditary hemorrhagic telangiectasia (HHT).

was diluted in 5 mL of normal saline for a final concentration of 10 mg/mL. For 2 consecutive weeks, following nasal irrigation with hypertonic saline delivered via a pulsatile nasal irrigator, 0.1 mL (1 mg) of the spray was delivered into each nostril twice each day. After 4 days (8 mg) the epistaxis ceased. Following 7 days of treatment (14 mg) no blood could be seen after nasal irrigation and bleeding was reduced to less than once a week.

Between 3 and 4 months after the above topical application, his epistaxis resumed. At first the epistaxis occurred once or twice a week and could be stopped with pressure only. It slowly increased in frequency and occurred almost daily, requiring cotton packing. Although the epistaxis worsened during this time period, it never became as severe as it had been prior to all VEGF inhibitor treatment. By the end of 4 months, the bleeding was similar to when the effect of the initial injection began to wane.

The patient decided to pursue a second course of topical treatment. Because of concerns for diluting and possible decay over time, the second treatment used off-the-shelf bevacizumab, 100 mg/4 mL. Placed in a nasal spray bottle was 1 mL (25 mg). Every 30 minutes 0.1 mL was sprayed into each nostril until the 25 mg was all sprayed. Bleeding once again ceased and has remained minimal for 2.5 months. The epistaxis severity score (ESS) has remained at 0.5, with only a slight increase to 1.07 in the month of September. ESS¹ for hereditary hemorrhagic telangiectasias is plotted using the HHT Foundation epistaxis severity score (Fig. 1 and Fig. 2).

DISCUSSION

HHT is an autosomal dominant disorder involving abnormal blood vessel development. Several genetic mutations have been identified in HHT patients. The

Summary Data Sheet

Patient Name:					
Date of Birth:					
Medical Record No.:					
	Date of ESS				
	/ /	/ /	/ /	/ /	/ /
Normalized ESS					
Raw ESS					
Treatment					
Factor					
Frequency					
Duration					
Intensity					
Medical Attention					
Anemia					
Transfusion					

Calculation:

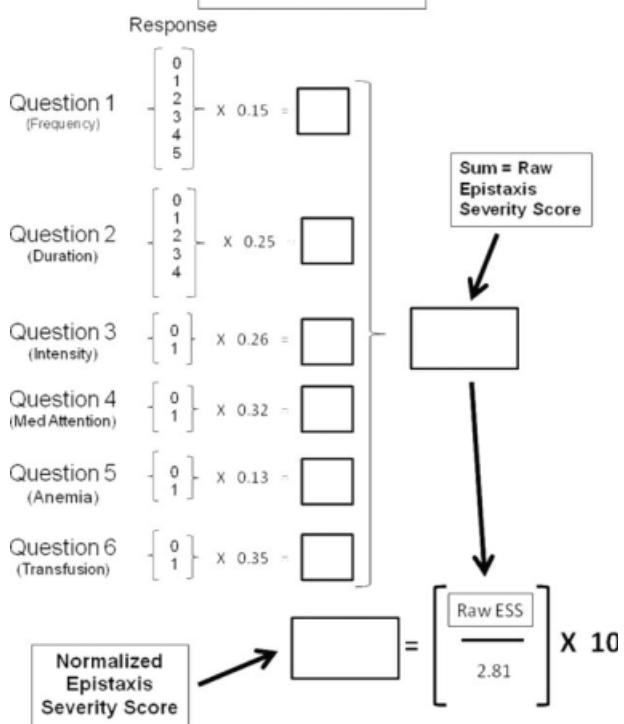


Fig. 1. (Continued)

role of these mutations in the development of telangiectasias and AVMs in patients with HHT is not yet well understood. It is believed that these mutations lead to an impairment of normal signaling pathways used for angiogenesis.² Recently, VEGF has been found to be elevated in HHT patients.³

Bevacizumab is a recombinant, humanized, monoclonal antibody that binds to and inhibits the activity of VEGF, which then prevents angiogenesis. It has been approved and effectively used for the treatment of metastatic colorectal cancer. When injected into the vitreous cavity, bevacizumab has been shown to lead to regression of the abnormal blood vessels that cause vision loss in patients with age-related macular degeneration (AMD).⁴ Intravitreal bevacizumab has been used in the treatment of neovascular glaucoma and retinopathy of prematurity.⁵ Topical bevacizumab has been used to treat neovascularization of the cornea.⁶ In each of these diseases, bevacizumab leads to regression of abnormal blood vessels by blocking VEGF production, which is assumed to be required not only for their development but for their continued presence.

Telangiectasias and AVMs may develop in the nose, brain, lungs, and gastrointestinal tract of patients with HHT. Epistaxis occurs in 90% of HHT patients and can lead to significant blood loss requiring IV iron, frequent emergency department visits, and blood transfusions. For those patients who experience significant epistaxis, treatment options include cauterization, septal dermoplasty, and closure of the nasal airway (Young's procedure). Although these treatments may be helpful, they often provide only temporary relief and/or may be associated with the morbidity of unwanted side effects, most commonly septal perforation.

If VEGF plays a role in the development of the telangiectasias that occur in HHT patients, bevacizumab may be useful in their treatment. Simonds et al. recently studied the role of bevacizumab as an adjunctive therapy to laser treatment in patients suffering from epistaxis due to HHT.⁷ They reported that patients receiving submucosal injections of bevacizumab at the time of laser treatment had less bleeding, required fewer blood transfusions, and had a greater improvement in their social life than those patients that underwent treatment with laser alone.

The rapidity of the response to the treatment in this case is impressive but follows a time course similar to that seen in the treatment of AMD and neovascular glaucoma.^{4,5} The dose of bevacizumab chosen to be used in this case was based upon the dose used in the submucosal bevacizumab injection study by Simonds et al.⁷ We initially employed a twice-a-day dosing schedule for

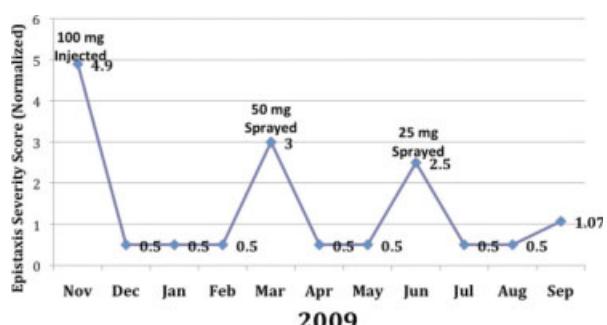


Fig. 2. Normalized epistaxis severity scores on y axis plotted against time in months on x axis.

convenience and to allow for irrigation to provide the best mucosal surface for drug absorption. The optimal dosing and treatment schedule is being investigated.

Reported complications of bevacizumab when used for colorectal cancer include impaired wound healing, hypertension, myocardial infarction, thromboembolism, and cerebral vascular accidents.⁸ Systemic doses used for the treatment of colon cancer are much larger than the dose used in this case. Cancer is generally treated with 5 mg/kg delivered intravenously every 2 weeks for 1 to 2 years. In a 70-kg patient this is 700 mg per month and 8,400 mg per year. Systemic risks following intravitreal injection, typically 1.25 mg, are debated. One large study of 4,303 injections did not show any significant increase in adverse events.⁹ To our knowledge there have been no documented systemic side effects of topical ocular administration. Our patient reported no side effects during his submucosal or topical treatments.

We report the first use of topical bevacizumab spray to treat recurrent epistaxis in a patient with HHT. The clinical and photographic results indicate that this may represent an exciting new option for these patients, which could possibly decrease the morbidity of current laser and surgical treatments. A topical nasal delivery system could also provide an option for earlier treatment for those patients not symptomatic enough to warrant surgical intervention. Further research is ongoing and will help determine optimal delivery and dosing.

CONCLUSION

VEGF inhibitors may be an exciting new treatment for HHT epistaxis.

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