CLINICAL VIGNETTE

A 45-Year-Old Woman with Hereditary Hemorrhagic Telangiectasia Successfully Treated with Bevacizumab

David Xu, MD and Zorawar Noor, MD

Case Presentation

A 45-year-old woman with hereditary hemorrhagic telangiectasia (HHT) presented to hematology to establish care. She was initially diagnosed with HHT at the age of 32 with daily epistaxis for much of her life. She was previously treated with laser cauterization of nasal blood vessels without major improvement. Exam included telangiectasias on her lips and tongue. She reported prior episodic gross hematuria and heavy menstrual bleeding with blood clots and hysterectomy at the age of 39. Over the years, she required intermittent intravenous iron therapy and did not have pulmonary or CNS arteriovenous malformations (AVMs). She underwent genetic testing at age 41, which confirmed the presence of heterozygous ACVRL1 mutation.

When she re-established hematology care, she reported 5 or more nosebleeds each day, which took approximately 20 minutes to completely control. She reported episodic vomiting of blood, but it was not clear if this was true hematemesis vs. vomiting of swallowed blood. She also reported severe exhaustion over the preceding six weeks. Her hemoglobin was 8.2. Iron studies were classic for iron deficiency. Because of prior intolerance of oral iron, she initially received 5 doses of iron sucrose with improvement but not normalization of the hemoglobin or iron indices. She received another course of iron sucrose with normalization of hemoglobin to 14.9 and near normalization of iron indices. Given the report of possible hematemesis, she underwent EGD which showed erythema in the gastric antrum but no evidence of recent bleeding in the stomach or presence of AVMs.

After discussion with the HHT Center interventional radiologist and hematology, the patient elected a trial of bevacizumab due to very frequent epistaxis leading to decreased quality of life as well as recurrent iron deficiency. Prior to starting bevacizumab, her iron deficiency anemia was already corrected with aggressive intravenous iron replacement therapy. She started every 2-week dosing of bevacizumab. After four weeks, her nosebleeds improved to 2-3 times a day. After 2 months on bevacizumab, she was down to 1-2 nosebleeds a day. After 3 months, she was getting a nosebleed 1-2 times a week and had no other bleeding symptoms. She transitioned to maintenance bevacizumab every 2-3 months and continues to tolerate it well without significant adverse effects.

Discussion

Hereditary hemorrhagic telangiectasia (HHT, also known as Osler-Weber-Rendu syndrome), is a genetic disorder of the vasculature that can affect multiple organ systems with bleeding as the most common problem. The most common types of bleeding are nosebleeds and GI bleeds. AVMs may develop in the lungs, liver, or the brain. The condition is uncommon, with prevalence between 1:5000 and 1:8000. Although HHT is inherited in an autosomal dominant fashion, there is varying penetrance and expression. This may lead to differences among relatives in the same family harboring the same pathogenic mutation. The most well-described gene mutations are found in *ENG*, *ACVRL1*, and *SMAD4*, which all cause a loss of function. These genes encode for proteins that are part of the bone morphogenetic protein signaling pathway, which if disrupted, leads to abnormal vascular remodeling and compromise of blood vessel wall integrity.

The classic clinical features of HHT include epistaxis, GI bleeding, and iron deficiency anemia as well as characteristic telangiectasia on the lips, oral mucosa, and fingertips. At least 50% of patients have pulmonary AVMs, which may lead to complications such as embolic strokes and brain abscesses, although actual hemorrhage is rare. About 10% may have cerebral AVMs. Liver AVMs may cause high-output heart failure. Telangiectasias and AVMs may form in the GI tract. Most patients have symptoms limited to epistaxis and mucocutaneous telangiectasia. Some may find the symptoms manageable, but others may have severe or frequent epistaxis and/or GI bleeds that significantly impact their quality of life. Severe iron deficiency anemia may require repeated intravenous iron replacement therapy or even transfusion dependence. Nosebleeds are often the first symptom in HHT, typically starting in childhood.

HHT is formally diagnosed based on the Curacao Criteria using clinical criteria OR by finding pathogenic mutation in an HHT gene. The Curacao diagnostic criteria include the following[1]:

- Spontaneous and recurrent epistaxis
- Multiple mucocutaneous telangiectasia at characteristic sites
- Visceral involvement (e.g. gastrointestinal telangiectasia; pulmonary, cerebral, or hepatic AVMs)
- A first-degree relative with HHT

Meeting 3 or 4 of the criteria is considered “definite” for HHT. While genetic testing is not absolutely required to diagnose HHT, the guidelines do suggest genetic testing for all patients who meet clinical criteria or those suspected of having HHT.

Iron replacement therapy is standard care for iron deficiency anemia from epistaxis and less commonly true GI bleeding. There are also therapies directed at the vascular lesions that aim to reduce the severity of bleeding. Bevacizumab in particular has been used for the management of severe bleeding in HHT patients. It was initially only recommended in guidelines for the most symptomatic patients. There is lack of robust data from prospective randomized trials to definitively support its use. The only prospective randomized trial for bevacizumab enrolled 24 patients who were randomized to either bevacizumab 5 mg/kg every 14 days for a total of 6 injections or placebo.[2] Seven out of eleven patients in the bevacizumab group and four out of twelve patients in the placebo group had > 50% decrease in the number of transfusions in the 3 months following treatment. While the percentage in the bevacizumab group was numerically higher, the difference did not reach statistical significance. Although the trial did not meet primary endpoints, hemoglobin levels were significantly improved at 6 months in patients who received bevacizumab as compared to those who received placebo.

In addition to the above RCT, there are nonrandomized, non-prospective data suggesting that bevacizumab may be beneficial in improving bleeding symptoms in HHT patients. One international retrospective study evaluated bevacizumab in the management of HHT-associated bleeding and anemia at 12 different HHT centers.[3] Two hundred thirty-eight patients were included, and they received bevacizumab on average for 12 months. The average pre-treatment hemoglobin was 8.6, and patients experienced on average hemoglobin increase of 3.2 with bevacizumab treatment in the first year. There was a corresponding decrease in the Epistaxis Severity Score by 3.4 points. In addition, all patients all had decreased transfusion dependence compared to 6 months before treatment as well as a decreased need for iron infusions. The most common side effects were fatigue, hypertension, proteinuria, and musculoskeletal aches, but bevacizumab was well tolerated overall. Venous thromboembolism (VTE) was reported in 2% of patients.

Another retrospective study looked at single center’s experience at Mayo Clinic HHT Center of Excellence. Thirty-four HHT patients were treated with bevacizumab who met criteria for severe epistaxis and/or GI bleed.[4] The median baseline hemoglobin was 9.1 and 47% of the patients were transfusion-dependent. Among all patients, 53% of patients required blood transfusion within 6 months of starting bevacizumab. This declined to 15% of patients requiring any transfusion after 1-3 months on bevacizumab, and eventually decreased to 9% after 9-12 months of bevacizumab therapy. Among the transfusion-dependent patients, 88% of patients had required transfusions in the 6 months preceding the start of bevacizumab therapy. Among those same patients, 31% of patients required any transfusion after 1-3 months of bevacizumab, and after 9-12 months, only 8% required any blood transfusion.

While high-quality studies are lacking to recommend the routine use of bevacizumab for any patients with HHT, the literature does reveal evidence of it being quite beneficial in select HHT patients. Those who are transfusion-dependent are more likely to have a favorable benefit/risk ratio from bevacizumab therapy. Even for those who are not transfusion-dependent but whose quality of life is severely negatively impacted by bleeding symptoms and the inconvenience of needing repeat iron infusions, may consider bevacizumab therapy while acknowledging the limited data and the potential risks associated with use. Risk of hemorrhage and thrombosis are prominently featured in the adverse effect profile of bevacizumab, when used in combination with other systemic therapies for metastatic solid tumors. Bleeding attributable to bevacizumab was not reported, and VTE was uncommon. Similarly, GI perforation was not observed.

REFERENCES

1. **Faughnan ME, Mager JJ, Hetts SW, Palda VA, Lang-Robertson K, Buscarini E, Deslandres E, Kasthuri RS, Lausman A, Poetker D, Ratjen F, Chesnutt MS, Clancy M, Whitehead KJ, Al-Samkari H, Chakinala M, Conrad M, Cortes D, Crocione C, Darling J, de Gussem E, Derksen C, Dupuis-Girod S, Foy P, Geisthoff U, Gossage JR, Hammill A, Heimdal K, Henderson K, Iyer VN, Kjeldsen AD, Komiyama M, Korenblatt K, McDonald J, McMahon J, McWilliams J, Meek ME, Mei-Zahav M, Olitsky S, Palmer S, Pantalone R, Piccirillo JF, Plahn B, Porteous MEM, Post MC, Radovanovic I, Rochon PJ, Rodriguez-Lopez J, Sabba C, Serra M, Shovlin C, Sprecher D, White AJ, Winship I, Zarrabeitia R**. Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. *Ann Intern Med.* 2020 Dec 15;173(12):989-1001. doi: 10.7326/M20-1443. Epub 2020 Sep 8. PMID: 32894695.
2. **Dupuis-Girod S, Rivière S, Lavigne C, Fargeton AE, Gilbert-Dussardier B, Grobost V, Leguy-Seguin V, Maillard H, Mohamed S, Decullier E, Roux A, Bernard L, Saurin JC, Saroul N, Faure F, Cartier C, Altwegg R, Laccourreye L, Oberti F, Beaudoin M, Dhelens C, Desvignes C, Azzopardi N, Paintaud G, Hermann R, Chinet T**. Efficacy and safety of intravenous bevacizumab on severe bleeding associated with hemorrhagic hereditary telangiectasia: A national, randomized multicenter trial. *J Intern Med*. 2023 Dec;294(6):761-774. doi: 10.1111/joim.13714. Epub 2023 Aug 23. PMID: 37592715.
3. **Al-Samkari H, Kasthuri RS, Parambil JG, Albitar HA, Almodallal YA, Vázquez C, Serra MM, Dupuis-Girod S, Wilsen CB, McWilliams JP, Fountain EH, Gossage JR, Weiss CR, Latif MA, Issachar A, Mei-Zahav M, Meek ME, Conrad M, Rodriguez-Lopez J, Kuter DJ, Iyer VN**. An international, multicenter study of

intravenous bevacizumab for bleeding in hereditary hemorrhagic telangiectasia: the InHIBIT-Bleed study. *Haematologica*. 2021 Aug 1;106(8):2161-2169. doi: 10.3324/haematol.2020.261859. PMID: 32675221; PMCID: PMC8327711.

4. **Iyer VN, Apala DR, Pannu BS, Kotecha A, Brinjikji W, Leise MD, Kamath PS, Misra S, Begna KH, Cartin-Ceba R, DuBrock HM, Krowka MJ, O'Brien EK, Pruthi RK, Schroeder DR, Swanson KL**. Intravenous Bevacizumab for Refractory Hereditary Hemorrhagic Telangiectasia-Related Epistaxis and Gastrointestinal Bleeding. *Mayo Clin Proc*. 2018 Feb;93(2):155-166. doi: 10.1016/j.mayocp.2017.11.013. Epub 2018 Jan 24. Erratum in: *Mayo Clin Proc*. 2018 Mar;93(3):396. doi: 10.1016/j.mayocp.2018.02.007. PMID: 29395350.