Intranasal Tranexamic Acid for the Treatment of Hereditary Hemorrhagic Telangiectasia: A Case Report and Review of Treatment Options

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Hereditary hemorrhagic telangiectasia (HHT) is an autosomal-dominant disorder. The disease has been formally characterized with epistaxis, cutaneous and mucosal telangiectases, a first-degree relative with HHT, and visceral lesions such as arteriovenous malformations (AVMs). Hereditary hemorrhagic telangiectasia has been underreported for many years. Wider recognition of this disorder in recent years has prompted researchers and physicians to recognize milder cases and focus on earlier treatment. This article highlights different treatments used to control epistaxis and screen for other complications associated with HHT.

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Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal-dominant disorder.[1] Hereditary hemorrhagic telangiectasia affects 1 in 5000 to 8000 individuals and is characterized by the Curaçao criteria consisting of epistaxis, cutaneous and mucosal telangiectases, a first-degree relative with HHT, and visceral lesions such as arteriovenous malformations (AVMs).[1,2] The number of patients diagnosed with HHT is increasing, although not all individuals with recurrent epistaxis have a family history of epistaxis. It is important to consider the diagnosis of HHT because epistaxis can be an early manifestation and these patients need to be screened for visceral AVMs.[3] Recognition of milder cases now suggests that this condition is far more common than was previously reported.[4] Early screening and close monitoring can help prevent life-threatening complications.

Case Report

A 63-year-old woman who was previously diagnosed with HHT 50 years prior presented with recurrent epistaxis as well as chronic anemia due to both epistaxis and gastrointestinal tract bleeds. She had a history of multiple blood transfusions and took epoetin alfa, vitamin B_{12}, and iron supplements to control the anemia. During her late teens, she noticed telangiectases developing on her hands, face, lower lip, and tongue. She also had AVMs in her liver, lungs, and gastrointestinal tract, but none in her brain, spleen, or adrenal glands, which also are associated with HHT. The patient's father, sister, and sons also had been diagnosed with HHT, as well as cousins on her father's side of the family. On examination, multiple telangiectases located on her lower lip, tongue, hard and soft palate, chin, nose, cheeks, forehead, palms, and soles were seen (Figure).

For treatment of her epistaxis, the patient initially was instructed to apply 5 drops (approximately 0.25 mL) of 100 mg/mL tranexamic acid nasal drops daily, as documented in another case.[5] After a few months without showing a substantial decrease in epistaxis, the patient tried a daily maintenance dose consisting of 1 drop of intranasal

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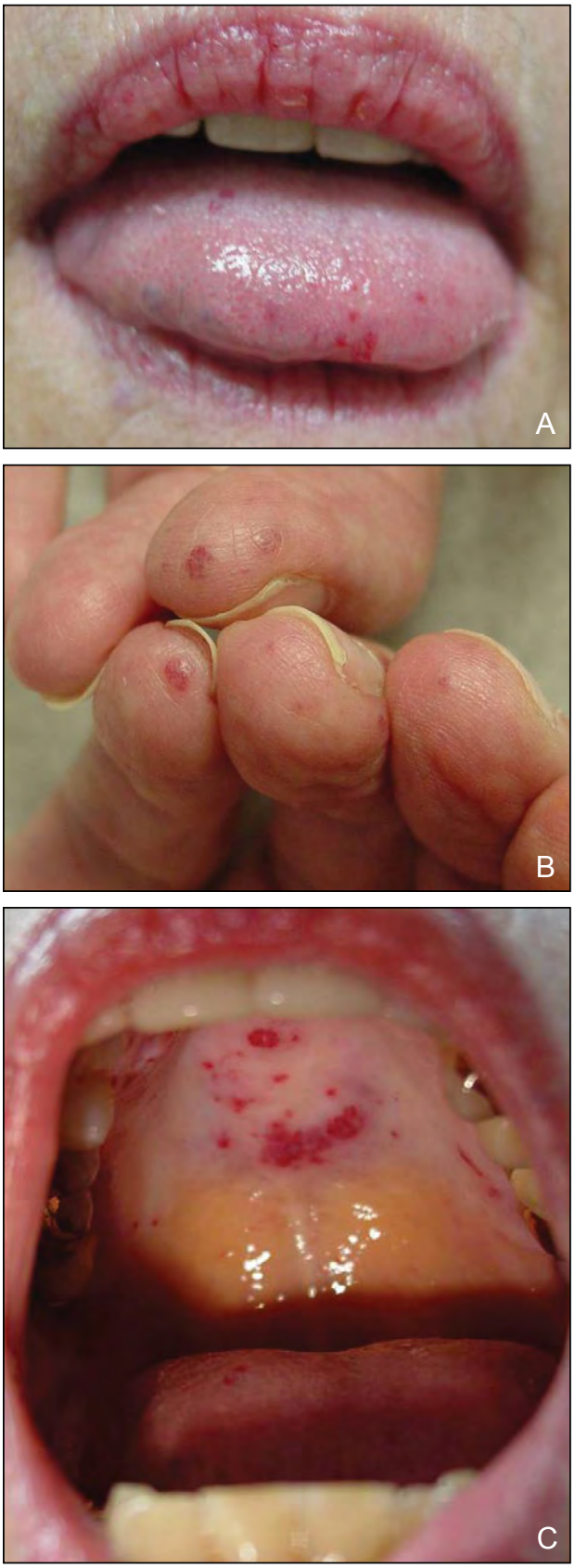

Telangiectases on the lips and tongue (A), fingertips (B), and palate (C).

tranexamic acid after completing the above regimen for episodes of epistaxis. This routine reduced her episodes of epistaxis from 3 to 4 times weekly to only 3 to 4 times monthly.

The patient also previously underwent intranasal KTP (potassium titanyl phosphate)(532 nm) laser treatment by an otolaryngologist to help control her epistaxis. Her facial telangiectases improved in appearance after treatment with a 595-nm pulsed dye laser every 1 to 2 months for 5 years. The patient elected to stop laser treatment of palmar telangiectases after she developed bleeding along with a pyogenic granuloma.

Comment

Hereditary hemorrhagic telangiectasia is a genetically heterogeneous disease involving 2 loci: HHT type 1 (HHT1), 9q34.11; and HHT type 2 (HHT2), 12q11-q14. The loci have been identified as endoglin, *ENG*, and activin receptor–like kinase 1, *ALK1*, of transforming growth factor β superfamily, respectively.[6] However, determining if patients have *ENG* or *ALK1* mutation does not predict the likely course of HHT because all features of HHT can be seen in both HHT1 and HHT2. It has been suggested that other genetic and environmental influences may modify the phenotypes. It is expected that the abnormal vessels in HHT develop because of aberrant transforming growth factor β signaling at some stage during vascular development and homeostasis.[2]

Patients with HHT should undergo a thorough medical evaluation, including radiographic imaging to document bleeding tract sites throughout the body. The combination of epistaxis, gastrointestinal tract bleeding, and iron deficiency anemia associated with characteristic telangiectasis on the lips, oral mucosa, and fingertips has become firmly established as a medical entity. However, the more well-known characteristics including epistaxis, anemia, and telangiectases of the mucous membranes can be minimal or absent in patients with HHT who still have life-threatening manifestations such as the AVMs seen with this disease.[2] These AVMs are most commonly seen in the lungs, gastrointestinal tract, and brain.[4] Hepatic AVMs also are commonly seen; therefore, imaging of the lungs, liver, gastrointestinal tract, and brain is an important part of the initial workup to treat and decrease the complications seen with HHT. The symptoms associated with HHT vary according to the location of the lesions.[7]

Epistaxis is one of the most common symptoms of HHT and often is recurrent, severe, and problematic to treat.[3] Currently, there is no definitive standard of treatment of HHT-associated epistaxis and the friable lesions of HHT may appear to bleed more with

treatment than without treatment. Numerous treatments have been used including electrocauterization, nasal packing, arterial ligation or embolization, systemic estrogens therapy, and even closure of the nostrils. Many of these techniques have adverse effects including ulcers and perforation. Another problem often seen with these techniques is the limited and short-lived success as well as the invasiveness of some of the procedures.

Because of the refractory nature of the epistaxis seen in HHT, researchers and physicians continue to develop novel therapeutic treatments for this disorder. In the last 20 years, multiple laser wavelengths including Nd:YAG, CO_2, argon, and KTP lasers have been used in the management of telangiectases in patients with HHT.[4] These lasers have the ability to specifically target the vasculature using laser photons that are absorbed by specific chromophores for different wavelengths. Selection of a laser system should be based on physician experience and preference. Because of the rarity of HHT, no randomized prospective studies have been performed comparing the results of treatment with use of these lasers.[4]

Few of these therapies have shown the efficacy demonstrated by the precise coagulation of telangiectases with laser treatment. Laser treatment has shown improvements in both the frequency and intensity of epistaxis in patients with HHT. The Nd:YAG laser (1064 nm) has a greater depth of penetration and greater zone of inflammation than either the argon (488–514 nm) or KTP (532 nm) lasers due to the differing wavelengths. A more extensive zone of inflammation increases the damage to the venous plexus, which is the origin of epistaxis in a patient with HHT. However, the limited penetration of the argon and KTP lasers provides for better protection of the underlying septal nasal cartilage.[8] Still, it is recommended that patients with severe epistaxis and diffuse intranasal vascular malformations may be better served by a more aggressive approach such as septodermoplasty.[4]

Many of the nasal cavity telangiectases can be controlled with conservative measures or frequent lasering. Currently, laser ablation of telangiectases has been the most widely used treatment option. Patients may need repeated treatments with this modality, but there is minimal mortality. Although laser therapies are suitable for smaller lesions, the treatment of larger, more coalescent lesions with lasers is challenging because treatment directed to the central lesion often results in high-flow bleeding from the coalescent lesion, making further ablation difficult.[9]

Bipolar cautery is another option with the potential advantage of allowing the larger lesions to be approached. Bipolar cautery offers a broad field of treatment due to the adjustable tines of the forceps. Also, physicians are able to avoid the potential iatrogenic laser injuries and treat at a much lower cost with the bipolar cautery technique. This technique has been documented as an effective treatment of general, non-HHT epistaxis in 2 prior studies.[10]

According to Kwaan and Silverman,[9] an increase in fibrinolytic activity has been demonstrated within the telangiectases of HHT. Tranexamic acid is an antihemophilia agent that forms a reversible complex that displaces plasminogen from fibrin, resulting in inhibition of fibrinolysis. It also inhibits the proteolytic activity of plasmin. The half-life of this product is 2 to 10 hours, and it is excreted in the urine.[6] This product is used for the prevention and control of bleeding in a variety of hemorrhagic diatheses.[11] Tranexamic acid was first demonstrated to be effective at reducing epistaxis in HHT in a study by Gage-White and LaMear. Unfortunately, they did not see any change to the hemoglobin level or improvement in the anemia.[12] Many physicians still believe that the anemia will correct if the epistaxis is under control.

A similar compound, aminocaproic acid, has been reported in a single case for the systemic treatment of HHT[12]; however, the systemic use of these compounds puts the patient at increased risk for thromboembolism. In another case report, it was suggested that immediately following the first sign of bleeding, 5 drops (approximately 0.25 mL) of 100 mg/mL tranexamic acid be applied as nasal drops.[5] Saba et al[13] reported that immediate control of bleeding usually followed, along with a marked decrease in the intensity of epistaxis, reducing the need for blood transfusions and iron supplements. Because the drops can be applied locally through nasal drops, there is a decrease in systemic exposure while delivering a high dose to the problematic area.

Conclusion

Hereditary hemorrhagic telangiectasia is a genetically inherited condition of small blood vessel malformations. Epistaxis is commonly refractory to treatment, with recurrent epistaxis seen in 50% to 80% of patients. The increased awareness and prevalence of the disorder is associated with the continued research and development for a treatment. Many treatment options are available, each with its positives and negatives; however, no studies have been conducted comparing their efficacy. Additionally, the treatment utilized is somewhat individualized to the patient's presentation and the physician's experience.

We found that when our patient tried the recommended 5 drops of 100 mg/mL tranexamic acid nasal drops applied locally to the nasal mucosa, she formed large clots in her nose. Therefore, we adjusted her

treatment to a daily application of 1 drop (Q-tip dab) in each nostril, which reduced her episodes of recurrent epistaxis from 3 to 4 times weekly to 3 to 4 times monthly. Until a definitive treatment is available, it appears that an individualized treatment plan will be the most efficient way to treat epistaxis in patients with HHT.

REFERENCES

1. Shovlin CL, Guttmacher AE, Buscarini E, et al. Diagnostic criteria for hereditary hemorrhagic telangiectasia (Rendu-Osler-Weber syndrome). *Am J Med Genet*. 2000;91:66-67.
2. Begbie ME, Wallace GM, Shovlin CL. Hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu syndrome): a view from the 21st century. *Postgrad Med J*. 2003;79:18-24.
3. Lung VJ, Howard DJ. A treatment algorithm for the management of epistaxis in hereditary hemorrhagic telangiectasia. *Am J Rhinol*. 1999;13:319-322.
4. Mahoney EJ, Shapshay SM. Nd-YAG laser photocoagulation for epistaxis associated with hereditary hemorrhagic telangiectasia. *Laryngoscope*. 2005;115:373-375.
5. Klepfish A, Berrebi A, Schattner A, et al. Intranasal tranexamic acid treatment for severe epistaxis in hereditary hemorrhagic telangiectasia. *Arch Intern Med*. 2001;161:767.
6. Corinaldesi G, Corinaldesi C. Strategy and management of upper bleeding in hereditary hemorrhagic telangiectasia: Rendu-Olser-Weber disease. *Am J Gastroenterol*. 2005;91:S53.
7. Peery WH. Clinical spectrum of hereditary hemorrhagic telangiectasia (Osler-Weber-Rendu disease). *Am J Med*. 1987;82:989-997.
8. Bergler W, Riedel F, Baker-Schreyer A, et al. Argon plasma coagulation for the treatment of hereditary hemorrhagic telangiectasia. *Laryngoscope*. 1999;109:15-20.
9. Kwaan HC, Silverman S. Fibrinolytic activity in lesions of hereditary hemorrhagic telangiectasia. *Arch Dermatol*. 1973;107:571-573.
10. Ghaheri BA, Fong KJ, Hwang PH. The utility of bipolar electrocautery in hereditary hemorrhagic telangiectasia. *Otolaryngol Head Neck Surg*. 2006;134:1006-1009.
11. Manucci PM. Hemostatic drugs. *N Engl J Med*. 1998;339:245-253.
12. Geisthoff J, Seyfert U, Konig J, et al. Hereditary hemorrhagic telangiectasia and tranexamic acid. *Otolaryngol Head Neck Surg*. 2003;129:203.
13. Saba HI, Morelli GA, Logrono LA. Brief report: treatment of bleeding in hereditary hemorrhagic telangiectasia with aminocaproic acid. *N Engl J Med*. 1994;330:1789-1790.