Case Report
DOI: http://dx.doi.org/10.47746/FMCR.2022.3204

Hereditary Hemorrhagic Telangiectasia in a Geriatric Patient: A Case of Treatment Resistance

Gregory A. Demirjian[1*] | Leila C. Tou[1] | Samantha E. Sugerik[1] | Taha A. Siddiqui[2] | Bernardo Reyes Fernandez[1]

***Correspondence:** Gregory A. Demirjian

Address: [1]Charles E. Schmidt College of Medicine, Florida Atlantic University, Boca Raton, FL, USA; [2]Philadelphia College of Osteopathic Medicine, Suwanee, GA, USA

e-mail ✉: gdemirjian2019@health.fau.edu

Received: 03 March 2022; **Accepted:** 18 April 2022

ABSTRACT

Hereditary hemorrhagic telangiectasia (HHT) is a condition known for frequent and severe epistaxis, telangiectasias that form along various surfaces of the body, and potentially life-threatening arteriovenous malformations (AVMs) that may develop in major organ systems. Management of this condition begins with prompt diagnosis, followed by careful screening for systemic complications, and care to minimize morbidity associated with blood loss. We hereby describe a case of treatment-resistant HHT in a geriatric patient who suffers from recurrent and severe epistaxis warranting frequent hospitalizations and blood transfusions. The case underscores the need to recognize HHT early, begin treatment promptly, and closely follow these patients to minimize the risk of hospital readmission.

Keywords: *HHT (Hereditary Hemorrhagic Telangiectasia), Osler-Weber-Rendu syndrome (OWRS)*

Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu Syndrome, is a rare genetic condition characterized by an autosomal dominant mutation in genes encoding for TGF-β receptors leading to the development of multiple arteriovenous malformations (AVM) (de Gussem *et al*., 2020). The prevalence of HHT is approximately 1 in 5,000 to 1 in 10,000 individuals as diagnosed using the Curaçao criteria (Iyer *et al*., 2016). A definitive diagnosis of HHT can be made if three of the four Curaçao criteria are met: (1) recurrent epistaxis, (2) multiple telangiectasias, (3) visceral AVMs, and (4) a family history of HHT (Table 1) (Mani *et al*., 2020; Garg *et al*., 2014). Spontaneous recurrent epistaxis due to the rupture of thin-walled nasal telangiectasias typically begins around 12 years of age and is seen in 90% of patients with HHT (de Gussem *et al*., 2020). Telangiectasias can occur prominently on the lips, fingers, tongue, and buccal mucosa. Visceral AVMs in patients with HHT can cause severe morbidity and

mortality. These AVMs may manifest in various organ systems including but not limited to the lungs, liver, brain, and gastrointestinal (GI) tract, with the lungs being the most common location (Mani *et al*., 2020). Mortality of HHT appears to have a bimodal distribution with a peak at age 50 and then from age 60-79, with most cases of mortality resulting from complications of AVMs, particularly in the brain, lungs, and GI tract (Iyer *et al*., 2016).

Table 1: Curacao Criteria for the Clinical Diagnosis of hereditary hemorrhagic telangiectasia (Garg *et al*., 2014).

Criteria	
Epistaxis	Spontaneous and recurrent nose bleeds
Telangiectasia	Multiple, at characteristic sites: lips, oral cavity, fingers and nose
Visceral Lesions	Includes gastrointestinal telangiectasias, or pulmonary, hepatic, cerebral, or spinal arteriovenous malformations
Family History	First-degree relative with HHT according to these criteria
The diagnosis is	
Definite	Three or more criteria are present
Possible or suspected	Two criteria are present
Unlikely	Fewer than two criteria are present
Abbreviations: HHT, hereditary hemorrhagic telangiectasia.	

With HHT, there exists a challenge of timely diagnosis. A 25-year diagnostic delay between symptom onset and confirmatory diagnosis of HHT was reported in one study surveying 233 patients with HHT, and approximately 10% of HHT patients develop severe HHT-related complications from the time of symptom onset to eventual diagnosis (Pierucci *et al*., 2012). The diagnosis of HHT is clinically challenging and its delayed diagnosis often leads to a worse prognosis. Even when diagnosed, the management of HHT is limited, and patients frequently experience a reduced quality of life due to recurrent epistaxis. This case report serves to aid clinicians in improving their understanding of HHT and its manifestations while highlighting current challenges in treating recurrent epistaxis in this patient population.

Case Presentation

An 80-year-old female with a past medical history of HHT, insulin-dependent Type II diabetes mellitus, hyperlipidemia, hypertension, and anxiety presented to the emergency department for an episode of bright red blood coming from the nose and mouth beginning spontaneously the night before being admitted to the hospital. She denied any trauma to the nose, any inhalation of medications, or use of illicit drugs through the nose. She tried applying pressure and ice without symptom resolution. She reports that the bleeding was unprovoked and appeared more severe compared to her previous episodes of nose bleeding, as this was the first time that she noticed bleeding from her mouth. However, she was not able to quantify how much blood she lost prior to arriving to the emergency department.

Medical history was significant for multiple hospitalizations due to epistaxis that warranted blood

transfusion. She was not taking aspirin at the time of the interview but has taken iron supplements and received iron infusions in the past for iron deficiency anemia. She was previously on Tamoxifen therapy for bleeding associated with her HHT with little benefit. In addition to cautery, she had endoscopic sinus surgery in 2017. The patient's chart showed endoscopy and colonoscopy performed in 2015 and 2017, respectively, with normal findings. Despite extensive workup, treatment attempts, and multiple visits to numerous HHT centers around the country, she has had little improvement in her condition.

On physical exam, the patient presented with a temperature of 97.2°F, heart rate of 69 beats per minute, and respiratory rate of 18 breaths per minute. Her blood pressure was 199/68 mmHg, and her oxygen saturation was at 93%. The patient was alert and oriented but appeared in mild distress. Extraocular movements were intact. Pupils were equal, round, and reactive to light and accommodation. A significant amount of blood was noted in the oropharynx, and the patient was actively spitting up blood. There was no evidence of active bleeding from the nose, but dried blood was noted in the nares bilaterally. She had a regular rate and rhythm with normal S1 and S2 sounds. No murmurs, gallops, or rubs could be auscultated. Lungs were clear to auscultation, and the chest was resonant to percussion bilaterally. She had normoactive bowel sounds with a soft, nondistended, nontender abdomen without guarding, rigidity, or rebound tenderness. Several telangiectasias were noted on the volar surface of her distal fingers, but there was no evidence of cyanosis, clubbing, or edema. Admissions labs were significant for leukocytosis of 11.9 ×103/μL, hemoglobin of 9.0 g/dL, and hematocrit of 28.1%.

The patient was admitted for epistaxis. Serial complete blood counts were ordered to trend hematocrit and hemoglobin with plans to transfuse as needed to maintain a hemoglobin greater than 7 g/dL. Hemoglobin (9.0 g/dL to 8.0 g/dL) and hematocrit (28.1% to 24.3%) decreased from admission values. The consulting otolaryngologist recommended oxymetazoline nasal spray every eight hours. Given the patient's elevated systolic blood pressure on admission, she was started on metoprolol and losartan which stabilized her blood pressures by the second day of admission. Initially, there were concerns for a possible GI bleed. However, bleeding improved throughout the day and completely ceased by day 2 of admission with hemoglobin and hematocrit stabilizing at 7.6 g/dL and 23.2%, respectively. The otolaryngologist discussed possible options for treatment which included further chemotherapy with the patient in the outpatient setting. She was cleared by the otolaryngologist for discharge home.

Discussion

Given the life-threatening complications of undiagnosed and untreated HHT, it is essential to have a timely diagnosis, and clinicians should have a high degree of suspicion in patients with a family history of HHT. Upon diagnosis of HHT, treatment is patient-specific, ranging from supportive care to lesion-

specific therapy and systemic treatment. In our patient, her frequent epistaxis warranted additional interventions such as electrocautery, sinus surgery, and trials of the specific estrogen receptor modulator (SERM) therapy with tamoxifen.

The management of epistaxis in HHT patients had recently been updated through the publication of the second international HHT guidelines in 2020 (Faughnan *et al*., 2020). The recommendation begins with the use of topical moisturizing therapies which improves the humidification of the nasal mucosa to reduce epistaxis severity, which is objectively measured by the epistaxis severity score (ESS) (Faughnan *et al*., 2020). For epistaxis that does not respond to topical moisturizing therapies, oral tranexamic acid has been shown to decrease epistaxis severity with minimal adverse effects (Faughnan *et al*., 2020). As an alternative to tranexamic acid, patients may employ ablative techniques such as laser treatment, radiofrequency, electrosurgery, and sclerotherapy which have been shown to temporarily reduce ESS. Patients that fail moisturizing therapies, ablative therapies and/or tranexamic acid may be offered one of three options that are based on moderate-to-low quality evidence: systemic antiangiogenic agents such as bevacizumab, septodermoplasty, or nasal closure (Faughnan *et al*., 2020). This patient had a history of nasal vessel cautery and endoscopic sinus surgery in 2017 with the hope of controlling her epistaxis. Unfortunately, these techniques were insufficient in providing her with symptomatic improvement.

Of note, the use of tamoxifen has been supported by a small number of cases. One such case discussed how tamoxifen therapy in HHT patients with mucosal bleeding may decrease the need for blood transfusion (Yung *et al*., 2021). Another case demonstrated long-term cessation of epistaxis in a postmenopausal woman with the use of tamoxifen therapy (Jameson *et al*., 2004). Nonetheless, the patient's treatment with tamoxifen was unsuccessful as she frequently returned to a private hospital six times in the last ten years for blood transfusions to treat anemia secondary to her epistaxis. As such, the otolaryngologist recommended outpatient follow-up with potential interest in starting chemotherapeutic agents. As bevacizumab is an antiangiogenic agent recommended for HHT, the patient may benefit from this medication in the future (Faughnan *et al*., 2020).

In addition to underscoring the need for improved therapies in HHT patients with epistaxis that is resistant to treatment, our patient's frequent hospital visits highlight the severe impact on healthcare costs and the quality of life for patients who experience similar refractory cases of HHT-related bleeding. Similarly, a population-based study of 840 patients hospitalized for epistaxis found HHT to be an independent predictor for readmission (OR = 13.216; CI 5.102–34.231) (Kallenbach *et al*., 2020). In this regard, there is a need for more population-based studies to better understand to what degree existing treatments for HHT truly reduce hospital readmission rates.

Conclusion

HHT is a rare genetic condition leading to epistaxis, telangiectasias, and AVMs posing a significant bleeding risk for those affected, particularly with increasing age. Traditional treatments of controlling epistaxis such as surgery and cauterization have limited success, often leading to the need for individualized treatment plans that commonly involve systemic medications and chemotherapy. This patient's clinical course highlights the limitations in guidelines for patients and the lack of resolution often faced (Faughnan *et al*., 2020). Further recognition of this condition with early treatment may help to delineate better options for these patients in the future. The treatment of HHT in the field of hematology-oncology is continually advancing and has great promise in reducing hospital readmission rates.

References

de Gussem E, Kroon S, Hosman A, Kelder J, Post M, Snijder R, Mager J. Hereditary hemorrhagic telangiectasia (HHT) and survival: the importance of systematic screening and treatment in HHT centers of excellence. *J Clin Med* 2020; 9: 3581.

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; 173: 989-1001.

Garg N, Khunger M, Gupta A, Kumar N. Optimal management of hereditary hemorrhagic telangiectasia. *J Blood Med* 2014;5: 191-206.

Iyer V, Brinjikji W, Pannu B, Apala D, Lanzino G, Cloft H, Misra S, Krowka M, Wood C, Swanson K. Effect of center volume on outcomes in hospitalized patients with hereditary hemorrhagic telangiectasia. *Mayo Clinic Proceedings* 2016; 91: 1753-1760.

Jameson JJ, Cave DR. Hormonal and antihormonal therapy for epistaxis in hereditary hemorrhagic telangiectasia. *Laryngoscope* 2004; 114: 705-709.

Kallenbach M, Dittberner A, Boeger D, Buentzel J, Kaftan H, Hoffmann K, Jecker P, Mueller A, Radtke G, Guntinas-Lichius O. Hospitalization for epistaxis: a population-based healthcare research study in Thuringia, Germany. *Eur Arch Otorhinolaryngol* 2020; 277: 1659–1666.

Mani B, Rubel A, Chauhdary W, Bashir A, Soe Z, Javed N, Sharif S, Hla Aye M, Chong V. Osler–Weber–Rendu syndrome. *QJM: An International Journal of Medicine* 2020; 113: 586-587.

Pierucci P, Lenato G, Suppressa P, Lastella P, Triggiani V, Valerio R, Comelli M, Salvante D, Stella A, Resta N, Logroscino G, Resta F, Sabbà C. A long diagnostic delay in patients with Hereditary Haemorrhagic Telangiectasia: a questionnaire-based retrospective study. *Orphanet J Rare Di* 2012; 7: 33.

Yung S, Bell JA, Brooker J. Tamoxifen therapy for recurrent mucosal bleeding in hereditary hemorrhagic telangiectasia. *J Hematol* 2021; 10: 22-24.