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CASE REPORT

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Hereditary hemorrhagic telangiectasia in a 42-year-old Ethiopian man presenting with severe anemia and high-output heart failure: A case report with literature review

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Key Clinical Messages

Hereditary hemorrhagic telangiectasia (HHT), a rare hereditary disorder, can cause recurrent massive epistaxis and gastrointestinal bleeding leading to severe anemia. Early diagnosis of HHT is essential to provide timely interventional therapies.

Abstract

HHT is a rare autosomal dominant hereditary disease that results in abnormal vasculogenesis in the skin, mucous membranes, and visceral organs such as the liver, lungs, and brain. Clinical diagnosis of HHT is made using the Curacao criteria, which include recurrent spontaneous nosebleeds, mucocutaneous telangiectasias, visceral organ involvement, and first-degree family history of HHT. Here, we report a patient with HHT from Ethiopia, who presented with recurrent epistaxis and gastrointestinal bleeding, and severe anemia requiring frequent blood transfusions as well as cauterization. The presented case is a 42-year-old Black Ethiopian man with frequent hospitalization for severe anemia and high-output heart failure requiring frequent blood transfusions. His mother had bilateral epistaxis since her early adulthood. Physical examination was significant for tachycardia, pale conjunctivae, and tiny erythematous lesions over his tongue, ejection systolic murmur and peripheral edema. Laboratory investigations revealed severe anemia with iron deficiency picture. Upper gastrointestinal endoscopy showed multiple telangiectasia spots and abdominal Doppler ultrasound showed hepatic arterio-venous malformations. He received supportive management and electrocauterization of nasal, gastric, and duodenal telangiectasias. To the best of our knowledge, this is the first case of HHT to be reported from Ethiopia. High degree of suspicion and early diagnosis of HHT is essential to start preventive screening and surveillance and provide timely interventional therapies. HHT can cause recurrent massive epistaxis and gastrointestinal bleeding leading to severe anemia and high-output heart failure. In resource limited

settings, selective cauterization of telangiectasia will help to control bleeding, although it does not avoid recurrent bleeding.

KEYWORDS

epistaxis, Hereditary hemorrhagic telangiectasia, high-output heart failure, severe anemia

1 | INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also referred to as the Osler–Weber–Rendu syndrome, is a rare autosomal dominant hereditary disease that results in abnormal vasculogenesis in the skin, mucous membranes, and visceral organs such as the liver, lungs, and brain.[1] The prevalence of HHT ranges from one in every 5000 people to 1 in every 8000 people with an estimated 85,000 cases in Europe[2,3] and the rate of diagnosis is lower in lower socioeconomic groups.[4]

Four important genes, including ENG (endoglin), ACVRL1 (activin receptor-like kinase 1), SMAD4 (mothers against decapentaplegic homolog 4), and GDF2 (growth differentiation factor 2), have recently been linked to the underlying mechanism of HHT.[5] Arterio-venous malformations (AVMs) are caused by mutations in these genes that interfere with the TGF-β (transforming growth factor)-beta signaling pathways in vascular endothelial cells, which impair cell division.[6] Heterozygous mutations are the common cause of the two primary kinds of HHT. Endoglin (ENG) is mutated in HHT1. Patients, especially women, with this type are more likely to develop pulmonary and cerebral AVMs. Activin A receptor-like type 1 (ACVRL1), commonly referred to as ALK1, is mutated in HHT2. Of the mutations known to cause HHT, ENG makes up around 61% and ACVRL1 makes up about 37%.[7,8]

About 90% of those with the condition experience recurrent nosebleeds, which usually begin in childhood. Other symptoms include gastrointestinal bleeding (25%–30%), which can cause melena and severe symptomatic microcytic anemia; pulmonary arteriovenous malformations (AVM) (50%) that can cause dyspnea, hemoptysis, paradoxical emboli, and cerebral abscesses; cerebral vascular malformations (10%) that can cause headache, seizures, and focal neurological deficits; and hepatic AVM (40%–70%), which are typically asymptomatic but might show signs of high-output heart failure and hepatic decompensation, ultimately necessitating liver transplantation.[9]

Clinical diagnosis of HHT is made using the Curacao criteria,[10] which include first-degree family history of HHT, visceral organ involvement, recurrent spontaneous nosebleeds, and mucocutaneous telangiectasias.

TABLE 1 Curaçao diagnostic criteria for hereditary hemorrhagic telangiectasia (HHT).

List of criteria	Number of criteria present	Likelihood of diagnosis
1. Recurrent spontaneous nosebleeds 2. Mucocutaneous telangiectasias 3. Visceral organ involvement 4. First-degree family history of HHT	≥3	Definite
	2	Suspected
	<2	Unlikely

If three or more criteria are met, the diagnosis of HHT is considered to be definite; if only two criteria are met, the diagnosis of HHT is suspected (Table 1). If less than two criteria are met, the diagnosis of HHT is considered to be unlikely.

Despite the recent advancements in understanding the genetic mechanisms and establishing the diagnostic criteria, diagnosis of HHT is often delayed.[11] It is estimated that one third of patients wait 1–5 years and 15% of patients wait 6 years or more for a correct diagnosis.[12] Timely diagnosis is essential for preventing and managing visceral complications and promoting adequate genetic testing and counseling for patients and families.

The clinical presentations of HHT determine its course of treatment. Sclerotherapy, oral tranexamic acid, nasal lubrication, or surgical ablation are all options for treating epistaxis. Patients with symptomatic liver AVM may require therapy for high-output heart failure and portal hypertension and the preferred course of treatment for refractory cases is liver transplantation. Endoscopic electrocauterization is used when there is gastrointestinal AVM hemorrhage. Serious cases of iron deficiency anemia are treated with blood transfusions and iron replacement. Tranexamic acid is administered intravenously or orally to treat refractory bleeding.[13,14]

Here, we report a patient with HHT from Ethiopia, who presented with recurrent epistaxis and gastrointestinal bleeding, and severe anemia requiring frequent blood transfusions as well as cauterization.

2 | CASE PRESENTATION

A 42-year-old black Ethiopian man presented to Yekatit 12 Hospital Medical College with a 2-day history of worsening of shortness of breath, which followed multiple episodes of massive bilateral epistaxis. He also noted lightheadedness, dizziness, tinnitus, easy fatigability, generalized body swelling which started from the legs, palpitation, orthopnea, and paroxysmal nocturnal dyspnea.

Further inquiry revealed history of bilateral nasal bleeding which initially started 6 years back. Over time, the epistaxis became more frequent and severe, sometimes bleeding up to 1 L per episode. He also had passage of black tarry stools for 7 months prior to his last visit. Before his current admission, he was hospitalized three times in the last 2 years, with diagnosis of high output heart failure secondary to severe anemia and received frequent blood transfusions. On his last admission, he received 5 units of packed red blood cells and was also given oral iron. His mother had epistaxis through bilateral nostrils which started in her early adulthood. She died of unknown cause at the age of 60.

Physical examination was significant for tachycardia (pulse rate of 106 beats per minute), pale conjunctivae and tiny erythematous lesions over the dorsum of his tongue which blanch on pressure (Figure 1), bibasilar lung rales, raised JVP, ejection systolic murmur at the apex, and pitting leg edema.

Upon laboratory investigations, complete blood count revealed hemoglobin of 4 g/dL (MCV 78 fL) and normal white blood cell and platelet counts; iron studies revealed low serum iron level of 20 μg/dL (reference range: 33–193 μg/dL) and low ferritin level of 16.8 ng/mL (reference range: 30–150 ng/mL); liver enzymes, renal function tests and coagulation profiles were with in normal limits. Peripheral blood smear showed microcytic and hypochromic anemia. Chest x-ray revealed Grade I pulmonary edema and borderline cardiomegaly, but echocardiography showed signs of high output heart failure with ejection fraction of 70%.

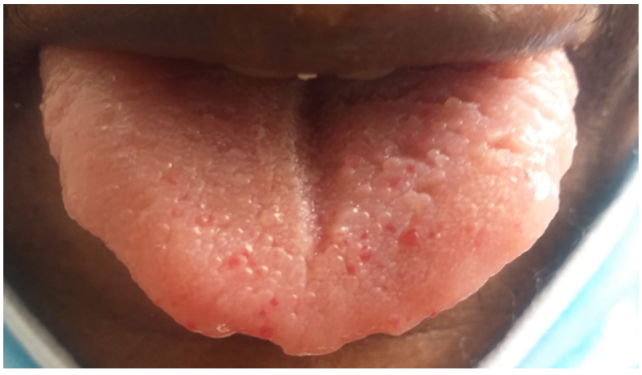

FIGURE 1 Multiple telangiectasias on the tongue.

Upper gastrointestinal (GI) endoscopy showed multiple telangiectatic spots in the stomach and duodenum oozing heme (Figure 2) while colonoscopy showed pale mucosa with normal vascular architecture. Abdominal ultrasound with Doppler study showed minimal bilateral pleural effusion and hepatic AVMs (Figure 3). Screening for pulmonary AVMs and cerebral vascular malformations (VMs), with contrast echocardiography and brain magnetic resonance imaging (MRI), was not done due to unavailability of such screening investigations in the hospital and financial constraints for work up in advanced private diagnostic centers.

He was frequently hospitalized because of the severe anemia and high-output heart failure; received frequent blood transfusions; put on diuretics and had nasal packing applied during episodes of nasal bleeding. He had marked improvement of heart failure symptoms and signs after correction of the severe anemia. Due to ongoing gastrointestinal bleeding, he was transferred to another hospital for endoscopic intervention where electrocauterization (electro-ablation) of gastric and duodenal telangiectasias was done (Figure 4), after which there was no drop in hemoglobin and he did not require transfusion. But then, he continued to have bouts of massive epistaxis for which silver nitrate cauterization was done, bleeding was arrested and septal dermoplasty was planned if any recurrence.

3 | DISCUSSION

Hereditary hemorrhagic telangiectasia (HHT, also known as Osler–Weber–Rendu syndrome) is characterized by the growth of AVMs on mucocutaneous surfaces, including the skin, lips, nose, and buccal mucosa, as well as visceral organs like the brain, lungs, and liver.[13] Recurrent epistaxis and mucocutaneous telangiectasias are the most prevalent clinical symptoms of HHT, occurring in more than 90% of affected people by the age of 40.[15]

By the time a patient reaches the age of 30,[16] telangiectasias are more prevalent, affecting 70% of individuals and infrequently bleed. Our patient's first episode of epistaxis occurred around the age of 36, which is a little later than what is generally described in the literature, which states that epistaxis is the disease's initial clinical manifestation in more than 90% of cases, and that it usually starts before the age of 20.[17]

Up to 30% of patients experience recurrent GI bleeding as a result of telangiectasias.[18] The upper GI endoscopy of our patient revealed numerous gastroduodenal telangiectasias and gastrointestinal hemorrhage. These results verified that our patient's GI telangiectasias are the sources of

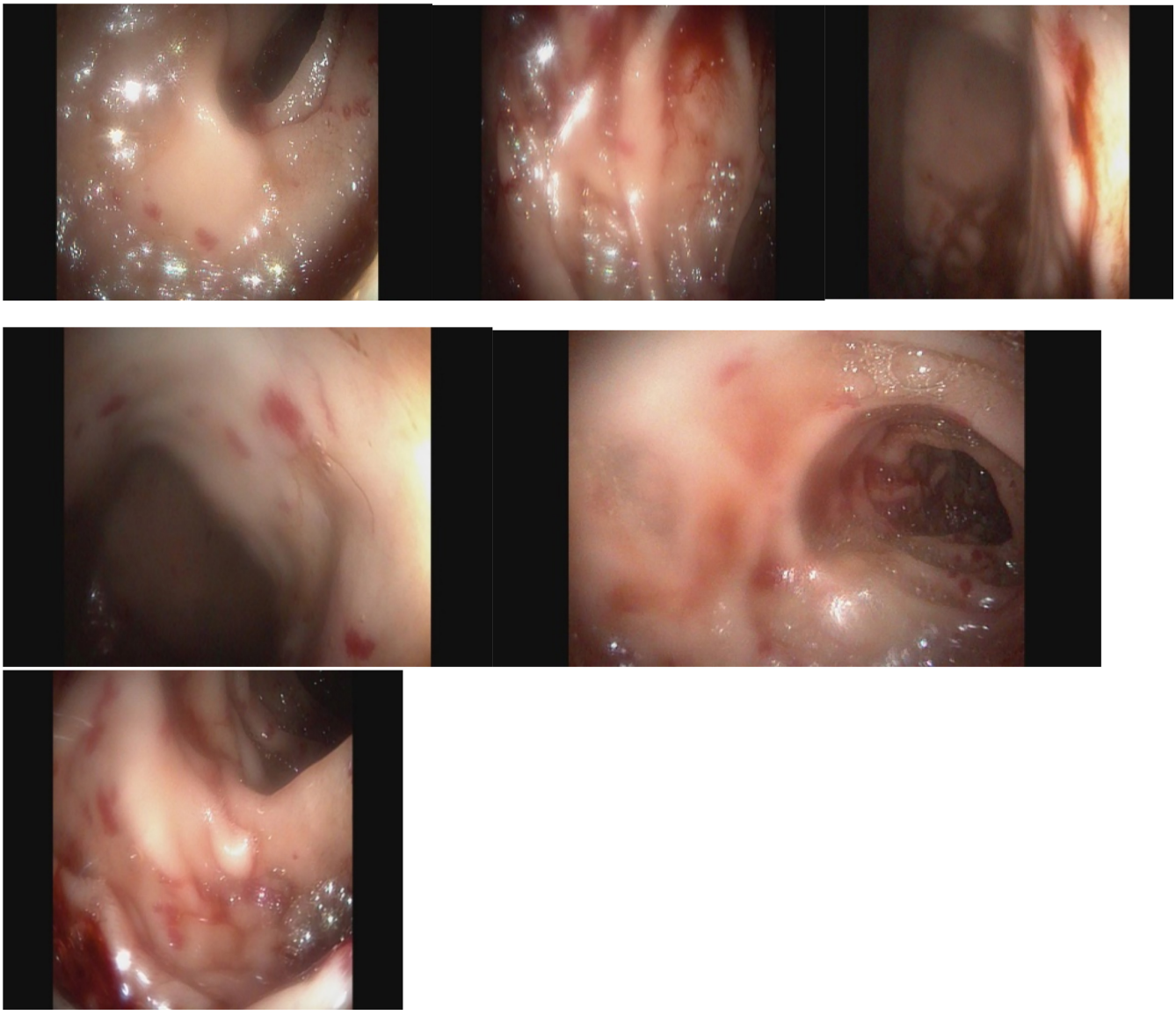

FIGURE 2 Upper gastrointestinal (GI) endoscopy showed multiple gastroduodenal telangiectasias.

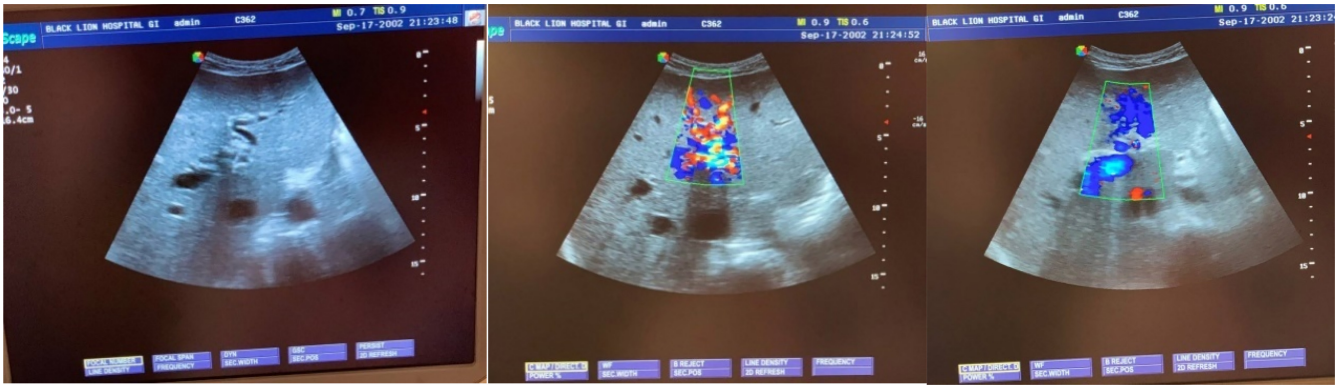

FIGURE 3 Abdominal Doppler ultrasound revealed hepatic arteriovenous malformations (AVMs).

bleeding. Gastrointestinal bleeding is often encountered in people who are in their fifth decade of life which goes with our patient's presentation.[19]

Severe anemia, as was discovered in our patient, is not a frequent finding in HHT. Anemia is primarily brought on by persistent gastrointestinal bleeding and,

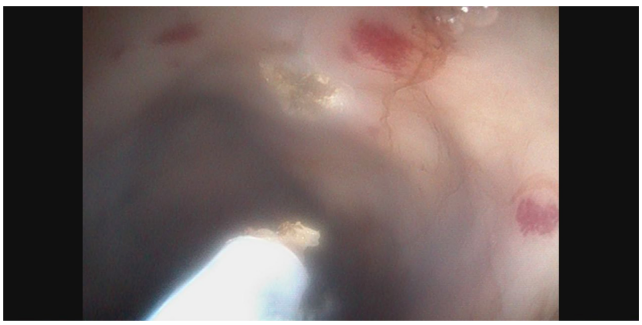

FIGURE 4 Endoscopic electrocauterization of telangiectasias.

in rare cases, severe epistaxis.[20] In a study to evaluate the prevalence and risk factors for anemia in HHT, epistaxis and gastrointestinal bleeding were both demonstrated to be independently connected with anemia, and the prevalence of a history of anemia was found to be 50%.[21] In line with the results of this study, our patient had severe anemia because of the epistaxis and gastrointestinal hemorrhage. In another study which included a total of 168 patients, 84 had documented anemia and of the patients with anemia, the majority were female (72%) and Caucasian (79%) unlike demography of our patient. GI telangiectasias were most common in the severe anemia group (67%) coinciding with findings of our patient.[22]

HHT rarely has an impact on the heart. High-output cardiac failure brought on by AVMs in the liver is the most prevalent condition.[23] In our patient, the hepatic AVMs might have increased the risk of developing high-output heart failure in the presence of the severe anemia. However, the hepatic AVMs could not be the predominant cause for the high-output heart failure as the patient had marked improvement of heart failure state after correction of the severe anemia.

Visceral AVMs, which are mostly asymptomatic, affect the cerebral, pulmonary, hepatic and, sporadically spinal vasculature.[24] Though our patient had hepatic AVMs demonstrated on abdominal Doppler ultrasound, he was not screened for pulmonary AVMs and cerebral VMs. However, the current standard practice in HHT centers is to routinely screen for pulmonary AVMs and brain VMs.[25]

The treatment of HHT is mainly conservative as there is no permanent cure for the bleeding and anemia. The therapy revolves around the prevention and acute management of these manifestations, including blood transfusions and iron supplementation. Our patient was getting supportive management with frequent blood transfusions and optimal diuresis along with per need nasal packing. When supportive management fails, newer therapies like hormonal agents, thalidomide and bevacizumab have shown promising results.[24] Bevacizumab produced a very strong response in two patients with HHT who also experienced epistaxis and GI bleeding, which significantly decreased the number of blood transfusions needed.[19,26]

A skilled endoscopist may consider making a few limited tries to cauterize big visible telangiectasias, but repeated attempts are not likely to be successful.[27,28] Our patient had undergone successful endoscopic intervention with numerous endoscopic electrocauterizations done using a snare tip for his stomach and duodenal telangiectasias after which he did not have a drop in hemoglobin level and was transfusion free.

4 | LIMITATIONS OF THE CASE REPORT

The patient was not screened for pulmonary AVMs and cerebral VMs with contrast echocardiography and brain MRI due to unavailability of such screening investigations in the hospital and financial constraints for work up in advanced private diagnostic centers.

5 | CONCLUSION

To the best of our knowledge, this is the first case of HHT to be reported from Ethiopia. High degree of suspicion and early diagnosis of HHT is essential to start preventive screening and surveillance and provide timely interventional therapies. HHT can cause recurrent massive epistaxis and gastrointestinal bleeding leading to severe anemia and high-output heart failure. In resource limited settings, selective cauterization of telangiectasia will help to control bleeding, although it does not avoid recurrent bleeding.

AUTHOR CONTRIBUTIONS

Gashaw Solela: Conceptualization; data curation; formal analysis; resources; writing – original draft; writing – review and editing. **Michael Adamseged:** Conceptualization; data curation; writing – original draft. **Abdulsemed Mohammed:** Validation; writing – review and editing.

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CONFLICT OF INTEREST STATEMENT

The authors declared no potential conflicts of interest.

DATA AVAILABILITY STATEMENT

The data that support this case report are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

Ethical clearance including publication of this patient's case details was obtained from the Institutional Review Board of Yekatit 12 Hospital Medical College.

CONSENT

The patient gave an informed written consent for the publication of his case details including the history, physical findings, laboratory reports and images.

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REFERENCES

1. Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. *Eur J Hum Genet*. 2009;17(7):860-871. doi:10.1038/ejhg.2009.35
2. Dakeishi M, Shioya T, Wada Y, et al. Genetic epidemiology of hereditary hemorrhagic telangiectasia in a local community in the northern part of Japan. *Hum Mutat*. 2002;19:140-148. doi:10.1002/humu.10026
3. Shovlin CL, Buscarini E, Kjeldsen AD, et al. European reference network for rare vascular diseases (VASCERN) outcome measures for hereditary haemorrhagic telangiectasia (HHT). *Orphanet J Rare Dis*. 2018;13:136. doi:10.1186/s13023-018-0850-2
4. Donaldson JW, McKeever TM, Hall IP, Hubbard RB, Fogarty AW. The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: a population-based study. *Thorax*. 2014;69(2):161-167. doi:10.1136/thoraxjnl-2013-203720
5. McDonald J, Stevenson DA. Hereditary Hemorrhagic Telangiectasia. In: Adam MP, Mirzaa GM, Pagon RA, et al., eds. *GeneReviews®*. University of Washington, Seattle; 2000 [Updated 2021 Nov 24] 1993–2023.
6. Macri A, Wilson AM, Shafaat O, Sharma S. *Osler-Weber-Rendu Disease*. StatPearls [Internet]; 2021.
7. Jackson SB, Villano NP, Benhammou JN, Lewis M, Pisegna JR, Padua D. Gastrointestinal manifestations of Hereditary hemorrhagic telangiectasia (HHT): a systematic review of the literature. *Dig Dis Sci*. 2017;62(10):2623-2630.
8. Morgan T, McDonald J, Anderson C, et al. Intracranial hemorrhage in infants and children with hereditary hemorrhagic telangiectasia (Osler-weber-Rendu syndrome). *Pediatrics*. 2002;109(1):E12.
9. Garg N, Khunger M, Gupta A, Kumar N. Optimal management of hereditary hemorrhagic telangiectasia. *J Blood Med*. 2014;5:191-206. doi:10.2147/JBM.S45295
10. Pahl KS, Choudhury A, Wusik K, et al. Applicability of the Curaçao criteria for the diagnosis of hereditary hemorrhagic telangiectasia in the pediatric population. *J Pediatr*. 2018;197:207-213. doi:10.1016/j.jpeds.2018.01.079
11. Sabbà C. A rare and misdiagnosed bleeding disorder: hereditary hemorrhagic telangiectasia. *J Thromb Haemost*. 2005;3(10):2201-2210.
12. Report of the National Commission on Orphan Disease. Executive Summary and Recommendations. US Department Of Health And Human Services 1989.
13. Hereditary LS. *Hemorrhagic Telangiectasia-NORD (National Organization for Rare Disorders)*. NORD (National Organization for Rare Disorders); 2021 Accessed May 10, 2022. rarediseases.org
14. Athena K, Al-Samkari H, Kuter DJ. Hereditary hemorrhagic telangiectasia: diagnosis and management from the hematologist's perspective. *Haematologica*. 2018;103(9):1-5.
15. Faughnan ME, Palda VA, Garcia-Tsao G, et al. International guidelines for the diagnosis and management of hereditary haemorrhagictelangiectasia. *J Med Genet*. 2011;48(2):73-87.
16. Plauchu H, Chadarévian D, Bideau A, Robert JM. Age-related clinical profile of hereditary hemorrhagic telangiectasia in an epidemiologically recruited population. *Am J Med Genet*. 1989;32(3):291-297.
17. Haitjema T, Balder W, Disch FJM, Westermann CJJ. Epistaxis in hereditary hemorrhagic telangiectasia. *Rhinology*. 1996;34:176-178.
18. Gallitelli M, Pasculli G, Fiore T, Carella A, Sabbà C. Emergencies in hereditary haemorrhagic telangiectasia. *QJM*. 2006;99(1):15-22.
19. Amanzada A, Töppler GJ, Cameron S, Schwörer H, Ramadori G. A case report of a patient with hereditary hemorrhagic telangiectasia treated successively with thalidomide and bevacizumab. *Case Rep Oncol*. 2010;3:463-470. doi:10.1159/000323152
20. dos Santos JWA, Dalcin TC, Neves KR, Mann KC, Pretto GLN, Bertolazi AN. Hereditary hemorrhagic telangiectasia: a rare cause of severe anemia. *J Bras Pneumol*. 2007;33(1):109-112.
21. Kasthuri RS, Montifar M, Nelson J, Kim H, Lawton MT, Faughnan ME. Brain vascular malformation consortium HHT Investigator Group. Prevalence and predictors of anemia in hereditary hemorrhagic telangiectasia. *Am J Hematol*. 2017;90(10):591-593. doi:10.1002/ajh.24832
22. Pahl K, Choudhury A, Kasthuri RS. Causes and severity of anemia in hereditary hemorrhagic telangiectasia. *Blood*. 2016;128(22):3776. doi:10.1182/blood.V128.22.3776.3776
23. Garcia-Tsao G, Korzenik JR, Young L, et al. Liver disease in patients with hereditary hemorrhagic telangiectasia. *N Engl J Med*. 2000;343:931-936.
24. Begbie M, Wallace G, Shovlin C. Hereditary haemorrhagic telangiectasia (Osler-weber-Rendu syndrome): a view from the 21st century. *Postgrad Med J*. 2003;79(927):18-24.
25. Kilian A, Clancy MS, Olitsky S, Gossage JR, Faughnan ME. Screening for pulmonary and brain vascular malformations is the north American standard of care for patients with hereditary hemorrhagic telangiectasia (HHT): a survey of HHT centers of excellence. *Vasc Med*. 2021;26(1):53-55.

26. Shovlin CL. Hereditary haemorrhagic telangiectasia: pathophysiology, diagnosis and treatment. *Blood Rev*. 2010;24:203-219. doi:10.1016/j.blre.2010.07.001
27. Bown SG, Swain CP, Storey DW, et al. Endoscopic laser treatment of vascular anomalies of the upper gastrointestinal tract. *Gut*. 1985;26(12):1338-1348.
28. Sargeant IR, Loizou LA, Rampton D, Tulloch M, Bown SG. Laser ablation of upper gastrointestinal vascular ectasias: long term results. *Gut*. 1993;34(4):470-475.

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