Brunei International Medical Journal

OFFICIAL PUBLICATION OF
THE MINISTRY OF HEALTH
AND
UNIVERSITI BRUNEI DARUSSALAM

Volume 18 26 February 2022 (25 Rejab 1443H)

EPISTAXIS, HEREDITARY HEMORRHAGIC TELANGIECTASIA AND IRON DEFICIENCY ANEMIA.

AHMED N[1], HLA AYE MT[2], CHOO S[1], MANI BI[2], KEASBERRY J[1], CHONG VH[1,2]

[1]Acute Medical Unit, Department of Medicine, RIPAS Hospital, Bandar Seri Begawan, Brunei Darussalam
[2]Department of Medicine, PMMPMHAMB Hospital, Jalan Sungai Basong, Tutong, Brunei Darussalam.

ABSTRACT

Iron deficiency anemia is commonly encountered in clinical practice and the underlying etiology can be benign or pathological, depending on the gender and age of patients. Common causes include pre-menopausal menstrual and gastrointestinal blood loss. However, it is important to be aware of less common causes. Hereditary hemorrhagic telangiectasia, also known as Osler-Weber-Rendu syndrome is disorder of vascular malformations that can affect any site. Hereditary hemorrhagic telangiectasia often manifest with chronic blood loss resulting in iron deficiency anemia. Telangiectasias affecting the hands and oral cavity can be easily detected on careful examination but can be overlooked. Vascular malformations affecting other sites such liver, lungs and brain require radiological imaging. We report two cases of hereditary hemorrhagic telangiectasia and iron deficiency anemia secondary to recurrent epistaxis, one patient requiring only iron supplementation to maintain hemoglobin level and another requiring frequent transfusion.

Keywords: Arteriovenous malformations, Epistaxis, Gastrointestinal blood loss, Iron deficiency anemia.

Brunei Int Med J. *2022;18:34-38*

ISSN 1560 5876 Print
ISSN 2079 3146 Online

Online version of the journal is available at www.bimjonline.com

Brunei International Medical Journal (BIMJ)
Official Publication of
The Ministry of Health
and
Universiti Brunei Darussalam

ISSN 1560-5876 Print
ISSN 2079-3146 Online

Aim and Scope of Brunei International Medical Journal

The Brunei International Medical Journal (BIMJ) is a six monthly peer reviewed official publication of the Ministry of Health under the auspices of the Clinical Research Unit, Ministry of Health, Brunei Darussalam.

The BIMJ publishes articles ranging from original research papers, review articles, medical practice papers, special reports, audits, case reports, images of interest, education and technical/innovation papers, editorials, commentaries and letters to the Editor. Topics of interest include all subjects that relate to clinical practice and research in all branches of medicine, basic and clinical including topics related to allied health care fields. The BIMJ welcomes manuscripts from contributors, but usually solicits reviews articles and special reports. Proposals for review papers can be sent to the Managing Editor directly. Please refer to the contact information of the Editorial Office.

Instruction to authors
Manuscript submissions
All manuscripts should be sent to the Managing Editor, BIMJ, Ministry of Health, Brunei Darussalam; e-mail: editor-in-chief@bimjonline.com. Subsequent correspondence between the BIMJ and authors will, as far as possible via should be conducted via email quoting the reference number.

Conditions
Submission of an article for consideration for publication implies the transfer of the copyright from the authors to the BIMJ upon acceptance. The final decision of acceptance rests with the Editor-in-Chief. All accepted papers become the permanent property of the BIMJ and may not be published elsewhere without written permission from the BIMJ.

Ethics
Ethical considerations will be taken into account in the assessment of papers that have experimental investigations of human or animal subjects. Authors should state clearly in the Materials and Methods section of the manuscript that institutional review board has approved the project. Those investigators without such review boards should ensure that the principles outlined in the Declaration of Helsinki have been followed.

Manuscript categories
Original articles
These include controlled trials, interventional studies, studies of screening and diagnostic tests, outcome studies, cost-effectiveness analyses, and large-scale epidemiological studies. Manuscript should include the following; introduction, materials and methods, results and conclusion. The objective should be stated clearly in the introduction. The text should not exceed 2500 words and references not more than 30.

Review articles

These are, in general, invited papers, but unsolicited reviews, if of good quality, may be considered. Reviews are systematic critical assessments of literature and data sources pertaining to clinical topics, emphasising factors such as cause, diagnosis, prognosis, therapy, or prevention. Reviews should be made relevant to our local setting and preferably supported by local data. The text should not exceed 3000 words and references not more than 40.

Special Reports

This section usually consist of invited reports that have significant impact on healthcare practice and usually cover disease outbreaks, management guidelines or policy statement paper.

Audits

Audits of relevant topics generally follow the same format as original article and the text should not exceed 1,500 words and references not more than 20.

Case reports

Case reports should highlight interesting rare cases or provide good learning points. The text should not exceed 1000 words; the number of tables, figures, or both should not be more than two, and references should not be more than 15.

Education section

This section includes papers (i.e. how to interpret ECG or chest radiography) with particular aim of broadening knowledge or serve as revision materials. Papers will usually be invited but well written paper on relevant topics may be accepted. The text should not exceed 1500 words and should include not more than 15 figures illustration and references

three relevant references should be included. Only images of high quality (at least 300dpi) will be acceptable.

Technical innovations

This section include papers looking at novel or new techniques that have been developed or introduced to the local setting. The text should not exceed 1000 words and should include not more than 10 figures illustration and references should not be more than 10.

Letters to the Editor

Letters discussing a recent article published in the BIMJ are welcome and should be sent to the Editorial Office by e-mail. The text should not exceed 250 words; have no more than one figure or table, and five references.

Criteria for manuscripts

Manuscripts submitted to the BIMJ should meet the following criteria: the content is original; the writing is clear; the study methods are appropriate; the data are valid; the conclusions are reasonable and supported by the data; the information is important; and the topic has general medical interest. Manuscripts will be accepted only if both their contents and style meet the standards required by the BIMJ.

Authorship information

Designate one corresponding author and provide a complete address, telephone and fax numbers, and e-mail address. The number of authors of each paper should not be more than twelve; a greater number requires justification. Authors may add a publishable footnote explaining order of authorship.

Group authorship

If authorship is attributed to a group (either solely or in addition to one or more individual authors), all members of the group must meet the full criteria and requirements for authorship described in the following paragraphs. One or more authors may take responsibility 'for' a group, in which case the other group members are not authors, but may be listed in an acknowledgement.

Authorship requirement

sign, and the analysis and interpretation of the data (where applicable); to have made substantial contributions to the writing or revision of the manuscript; and to have reviewed the final version of the submitted manuscript and approved it for publication. Authors will be asked to certify that their contribution represents valid work and that neither the manuscript nor one with substantially similar content under their authorship has been published or is being considered for publication elsewhere, except as described in an attachment. If requested, authors shall provide the data on which the manuscript is based for examination by the editors or their assignees.

Financial disclosure or conflict of interest

Any affiliation with or involvement in any organisation or entity with a direct financial interest in the subject matter or materials discussed in the manuscript should be disclosed in an attachment. Any financial or material support should be identified in the manuscript.

Copyright transfer

In consideration of the action of the BIMJ in reviewing and editing a submission, the author/s will transfer, assign, or otherwise convey all copyright ownership to the Clinical Research Unit, RIPAS Hospital, Ministry of Health in the event that such work is published by the BIMJ.

Acknowledgements

Only persons who have made substantial contributions but who do not fulfill the authorship criteria should be acknowledged.

Accepted manuscripts

Authors will be informed of acceptances and accepted manuscripts will be sent for copyediting. During copyediting, there may be some changes made to accommodate the style of journal format. Attempts will be made to ensure that the overall meaning of the texts are not altered. Authors will be informed by email of the estimated time of publication. Authors may be requested to provide raw data, especially those presented in graph such as bar charts or figures so that presentations can be constructed following the format and style of the journal. Proofs will be sent to authors to check for any mistakes made

EPISTAXIS, HEREDITARY HAEMORRHAGIC TELANGIECTASIA AND IRON DEFICIENCY ANEMIA.

AHMED N[1], HLA AYE MT[2], CHOO S[1], MANI BI[2], KEASBERRY J[1], CHONG VH[1,2]

[1]Acute Medical Unit, Department of Medicine, RIPAS Hospital, Bandar Seri Begawan, Brunei Darussalam
[2]Department of Medicine, PMMPMHAMB Hospital, Jalan Sungai Basong, Tutong, Brunei Darussalam.

ABSTRACT

Iron deficiency anemia is commonly encountered in clinical practice and the underlying etiology can be benign or pathological, depending on the gender and age of patients. Common causes include pre-menopausal menstrual and gastrointestinal blood loss. However, it is important to be aware of less common causes. Hereditary hemorrhagic telangiectasia, also known as Osler-Weber -Rendu syndrome is disorder of vascular malformations that can affect any site. Hereditary hemorrhagic telangiectasia often manifest with chronic blood loss resulting in iron deficiency anemia. Telangiectasias affecting the hands and oral cavity can be easily detected on careful examination but can be overlooked. Vascular malformations affecting other sites such liver, lungs and brain require radiological imaging. We report two cases of hereditary hemorrhagic telangiectasia and iron deficiency anemia secondary to recurrent epistaxis, one patient requiring only iron supplementation to maintain hemoglobin level and another requiring frequent transfusion.

Keywords: Arteriovenous malformations, Epistaxis, Gastrointestinal blood loss, Iron deficiency anemia.

INTRODUCTION

Iron deficiency anemia (IDA) is commonly encountered in clinical practice and the underlying etiology can be benign or pathological, depending on the gender and age of patients. In pre-menopausal women, menstrual blood loss is a common cause whereas in older persons regardless of gender, gastrointestinal blood loss from ulcer disease and neoplasms are common. However, it is important for clinicians to be aware of less common causes. Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder with disorganized angiogenesis that result in vascular malformations that affect the skin, mucus membranes and solid organs (i.e. liver, lung and brain).[1-3] Clinical manifestations of HHT include recurrent bleeding (i.e. epistaxis, hematemesis and hematochezia) resulting in IDA, and complications of shunting (i.e. high output cardiac failure, pulmonary hypertension and cerebral abscesses).[3-5] We report two cases of HHT, one needing frequent transfusions and another only needing maintenance

Corresponding author: Dr Justin Fook Siong Keasberry, General and Acute Medicine Physician, Acute Medical Unit, Department of Medicine, RIPAS Hospital, Jalan Putera Al-Muhtadee Billah, Bandar Seri Begawan BA1712, Brunei Darussalam.
E mail: jkeasberry@hotmail.com / justin_keasberry@moh.gov.bn
Phone: 224 2424

iron replacement therapy and in both cases, the diagnoses were delayed.

CASE REPORT

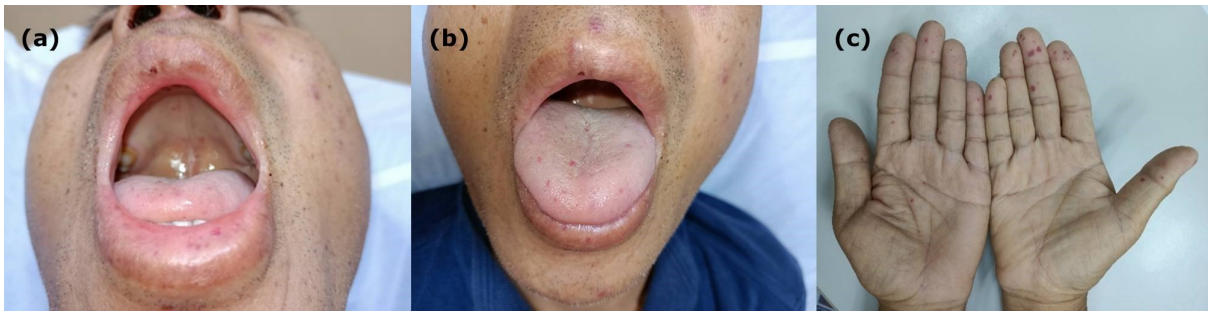
CASE 1 is a 58-year-old man who was admitted with spontaneous epistaxis from his right nostril of 1.5 hours duration. He also reported dizziness and lethargy from IDA. His co-morbidities include chronic hepatitis B, hypertension and dyslipidemia and recurrent episodes of epistaxis with similar presentations over the years requiring admission and transfusions. Physical examination revealed obvious multiple telangiectasia on his lips, palate (Figure 1: a-c), hands, face, and scalp. He also has multiple telangiectasias over his lip and inside his oral cavity. Admission investigation revealed serum hemoglobin level of 5.9 gm/dL (normal range 13.5-17.9), hematocrit 21.6% (41.6 – 53) and mean cell volume 62.7 (81-95.4). He was treated with intravenous tranexamic acid and blood transfusions.

A detailed review of his medical record revealed that he had frequent admissions approximately every two months for symptomatic IDA, each time preceded by prolonged epistaxis. He was already diagnosed with HHT for several years and was followed up in another institution. He also had local ablative therapies to the nasal cavity and on one occasion required angiography embolization to arrest bleeding. Previous endoscopies revealed several telangiectasias in the stomach and duodenum and none in the colon. However, these were not the cause of IDA. Computed tomography scan also revealed a hepatic vascular malformation, but none in the brain and lungs. He was previously treated with a course of intravenous bevacizumab, a vascular endothelial growth factor (VEGF) blocker, with little impact on the telangiectasias and frequency of bleeding and blood transfusions. On latest occasion, it was decided to initial a trial of thalidomide therapy. His family members were also screened clinically and with hepatic ultrasound and did not have evidence of HHT.

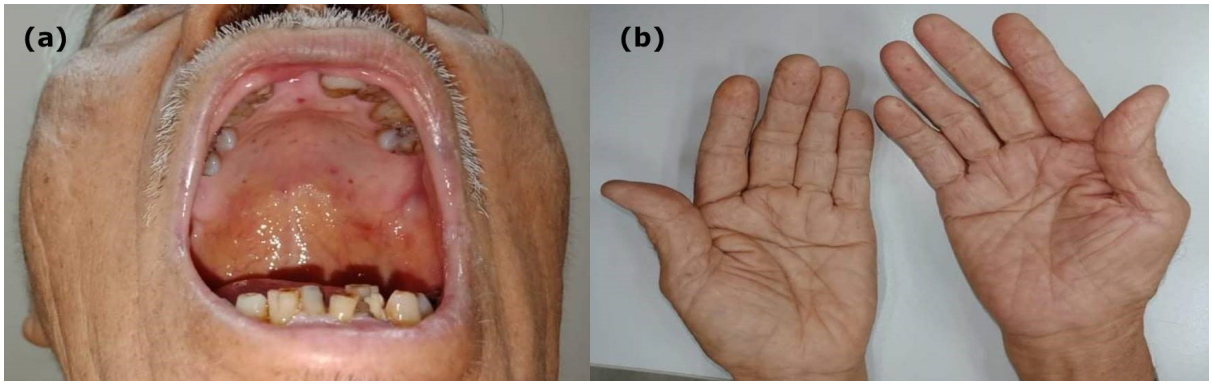
CASE 2

A 72-year-old man with IDA secondary to HHT was seen in the outpatient clinic. He remained well without any symptoms of anemia, and serum hemoglobin remained stable (between 10.0 to 11.0 g/dL) on iron replacement therapy. He continued to have epistaxis but less frequent with advice on nasal care aim at reducing trauma and drying of nasal mucosa. These episodes were self-limiting not requiring presentation to the doctors. Physical examination revealed numerous subtle telangiectasias in the palate, tongue and fingers (Figures 2).

He was previously admitted once a few years ago when he presented with symptomatic IDA (hemoglobin 4gm/dl, normal range 12.5 to 17.0). Prior to this admission, he was treated for IDA with intermittent iron replacement by his usual care doctor in the



Figures 1: Telangiectasias seen on the lip and palates (a), tongue (b) and fingers (c) in Case 1. (Click to enlarge)



Figures 2: Subtle telangiectasias seen over the palates (a) and fingers (b) in Case 2. (Click to enlarge)

outpatient clinic for several years but not diagnosed with HHT. He denied any history of upper or lower gastrointestinal symptoms and reported no warning symptoms such as melena, bleeding per rectum or weight loss. At admission, no telangiectasias were noted. He was treated with intravenous tranexamic acid and blood transfusion. Upper gastrointestinal endoscopy also showed several arteriovenous malformations in the stomach, and duodenum. Repeat clinical examination after transfusion then revealed multiple telangiectasias affecting the lip, oral cavity, hands, and feet. Colonoscopy was incomplete due to left inguinal hernia but examination to the sigmoid was otherwise normal. Computer tomography scan of the abdomen showed was normal apart from diverticular disease. Otorhinolaryngology examination revealed multiple telangiectasias in nasal cavities and over left torus tubaris. The patient had CT scans of the brain and chest which confirmed presence of pulmonary and intracranial AVMs. He was referred to neurosurgeons and thoracic surgeons for further follow-ups. His children also had nasal and clinical examinations and did not display any telangiectasias.

DISCUSSION

HHT is a rare genetic disorder with an autosomal dominant mode of inheritance with varying penetrance and expression. Three major disease-associated genes have been recorded which classify HHT into several subtype; 1) ENG (HHT1); 2) ACVRL1 (HHT2) and 3) SMAD4 (JPHT). [6, 7] However, there are more than 600 different pathogenic or likely pathogenic variants described, with none particularly common in different HHT families across the globe. [8] Pulmonary, and cerebral vascular malformations are more common in HHT1 patients, while hepatic AVMs and pulmonary arterial hypertension are more common in those with HHT2, both in adults and in children. [6, 7, 9]

The prevalence of HHT is reported to be around 1:8,000 with higher rates in isolated populations of 1:1,300 e.g., Curacao residents. [10-12] Based on these reported rates, we expect to see more cases but to our knowledge based on database search, these are the only two patients known, reflecting either the condition is uncommon in our setting, or many are undiagnosed. Furthermore, the true rates are likely to be higher as majority of patients may be unaware of their condition and have mild disease, coupled with lack of awareness among clinicians resulting in diagnosis being missed. [9, 13]

The pathogenesis of HHT is due to a dysfunction in the transforming growth factor beta signaling pathway resulting in abnormal vascular remodeling and disruption of blood vessel wall integrity. [1, 6, 7] Vascular malformations usually develop in the adulthood and may increase in number and size depending on the genetic defects. The larger malfor-

mations are prone to rupture due to trauma or elevated pressure and manifest with bleeding from commonly affected sites.

Epistaxis, typically recurrent is the most frequent clinical manifestation with an estimate of up to 96% of reporting epistaxis as the first symptom to appear. [4] This can be mild to severe as in our two cases. Although less common, bleeding can occur from other affect sites resulting occult to overt gastrointestinal bleeding to severe resulting in stroke. Paradoxical embolism through large pulmonary shunts has also been reported resulting in stroke and infection. [3-5]

Diagnosis of HHT is based on the Curaçao's diagnostic criteria which include spontaneous or recurrent epistaxis, telangiectasias at multiple sites, visceral vascular malformations, and a dominant familial aggregation. [1] At least three must observed to confirm a definite diagnosis. A diagnosis can be made by genetic tests. [1, 2, 4, 5] Our first patient has three criteria whereas our second patient has two criteria met. We did not do genetic testing as this is not available locally. Furthermore, genetic testing would not alter the immediate and long-term management. We have advised family members to present themselves if they noted any vascular lesions or experience any recurrent bleeding in particular epistaxis. Telangiectasias even the small and subtle ones can be detected during careful physical examination. Diagnoses of HHT were delayed in both patients having been treated for IDA.

Management depends on the severity of manifestations. [1, 4] Management is targeted towards prevention and control of bleeding and treatment of anemia or targeted at the vascular malformations. For milder presentations, iron supplementation and advise on measures to reduce epistaxis (control of blood pressure, avoidance of nasal trauma and maintenance of nasal mucosal integrity) may be adequate. For severe cases however, ablative therapies (local or system) may be indicated. For lesions in solid organs, close monitoring is advised and prophylactic eradication (surgery or vascular embolic ablative therapies) may be indicated if risk of complications is high. Bevacizumab and thalidomide have been used to manage HHT [14] with the aim of reducing the duration and intensity of epistaxis, increasing the quality of life and reducing transfusion needs as shown in phase two human trials and as per the current expert guidelines.[1] Our first case appeared to have limited or no response to several bevacizumab in terms of reduction of his transfusion requirements and epistaxis.

Currently the aforementioned patient is having a trial of moderate dose thalidomide therapy which was found in small trials to greatly reduced transfusion needs and increase haemoglobin levels with only minor adverse effects reported as seen in phase 2 trials. [15]

In regards to familial screening, the current expert guidelines recommend genetic testing and clinical screening for HHT diagnosis, primarily for asymptomatic persons from a family with known HHT. Additionally, screening is recommended for family members with HHT for pulmonary at cerebral AVMs at the time of diagnosis. [1]

CONCLUSION

In conclusion, our two cases highlight varied clinical manifestations and management of HHT, one with subtle lesions that could be easily missed and another with obvious lesions. Accurate and early diagnosis is essential. However, diagnosis is often delayed or missed due to lack of awareness even when lesions are present. Patients with or suspected to have HHT should be screened for vascular malformations in the other organs. For milder cases, iron supplementation with ad-

vice on nasal care may be adequate but for patients with larger lesions, shared care with specialist center is advised.

CONFLICTS OF INTEREST STATEMENT

The authors have no conflicts of interest to declare and consent has been obtained from patient and hospital authority to publish this article.

REFERENCE

1: Faughnan M, Mager J, Hetts S, et al. Second International Guidelines for the Diagnosis and Management of Hereditary Hemorrhagic Telangiectasia. Annals of Internal Medicine. 2020. DOI: 10.7326/M20-1443. [Accessed on 2022 February 18].

2: Letteboer TG, Mager HJ, Snijder RJ, et al. Genotype-phenotype relationship for localization and age distribution of telangiectasias in hereditary hemorrhagic telangiectasia. Am J Med Genet A. 2008;146A(21):2733–9.

3: Abdalla SA, Geisthoff UW, Bonneau D, et al. Visceral manifestations in hereditary haemorrhagic telangiectasia type 2. J Med Genet. 2003;40:494–502. [Accessed on 2022 February 18].

4: Kritharis A, Al-Samkari H, Kuter DJ. Hereditary hemorrhagic telangiectasia: diagnosis and management from the hematologist's perspective. Haematologica. 2018;103:1433–43. [Accessed on 2022 February 18].

5: 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. [Accessed on 2022 February 18].

6: Lesca G, Olivieri C, Burnichon N, et al. Genotype-phenotype correlations in hereditary hemorrhagic telangiectasia: data from the French-Italian HHT network. Genet Med. 2007;9:14. [Accessed on 2022 February 18].

7: Bossler AD, Richards J, George C, et al. Novel mutations in ENG and ACVRL1 identified in a series of 200 individuals undergoing clinical genetic testing for hereditary hemorrhagic telangiectasia (HHT): correlation of genotype with phenotype. Hum Mutat. 2006; 27:667.

8: Shovlin CL, Simeoni I, Downes K, et al. Mutational and phenotypic characterization of hereditary hemorrhagic telangiectasia. Blood. 2020;136:1907. [Accessed on 2022 February 18].

9: Kilian A, Latino GA, White AJ, et al. Genotype-Phenotype Correlations in Children with HHT. J Clin Med. 2020;9. [Accessed on 2022 February 18].

10: 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. [Accessed on 2022 February 18].

11: Westermann CJ, Rosina AF, De Vries V, de Coteau PA. The prevalence and manifestations of hereditary hemorrhagic telangiectasia in the Afro-Caribbean population of the Netherlands Antilles: a family screening. Am J Med Genet A. 2003;116A:324.

12: Donaldson JW, McKeever TM, Hall IP, et al. The UK prevalence of hereditary haemorrhagic telangiectasia and its association with sex, socioeconomic status and region of residence: a population-based study. Thorax. 2014;69:161. [Accessed on 2022 February 18].

13: Govani FS, Shovlin CL. Hereditary haemorrhagic telangiectasia: a clinical and scientific review. Eur J Hum Genet. 2009;17:860. [Accessed on 2022 February 18].

14: Robert F, Desroches-Castan A, Bailly S, Dupuis -Girod S, Feige JJ. Future treatments for hereditary hemorrhagic telangiectasia. Orphanet J Rare Dis. 2020;15:4. doi: 10.1186/s13023-019-1281-4. [Accessed on 2022 February 18].

15: Invernizzi R, Quaglia F, Klersy C, et. al. ini CL. Efficacy and safety of thalidomide for the treatment of severe recurrent epistaxis in hereditary haemorrhagic telangiectasia: results of a non-randomised, single-centre, phase 2 study. Lancet Haematol. 2015;2(11):e465-73. doi: 10.1016/S2352-3026(15)00195-7. [Accessed on 2022 February 18].