Research Article

ISSN 2833-0307

Endocrinology, Metabolism and Nutrition

Gastrointestinal Complications of Hereditary Haemorrhagic Telangiectasia: Unravelling the Potential Link with Protein Losing Enteropathy

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Received: 09 Feb 2024; **Accepted:** 14 Mar 2024; **Published:** 20 Mar 2024

Citation: Bhandari R, Ekladious A, Javaid MM, et al. Gastrointestinal Complications of Hereditary Haemorrhagic Telangiectasia: Unravelling the Potential Link with Protein Losing Enteropathy. Endocrinol Metab Nutr. 2024; 3(1): 1-12.

ABSTRACT

This comprehensive review delves into the clinical features of Hereditary Haemorrhagic Telangiectasia (HHT), with a specific emphasis on gastrointestinal manifestations. The exploration centres on a unique case presenting with Protein Losing Enteropathy (PLE). Historically, PLE has not been documented as a recognized complication of HHT, making this case an unprecedented and intriguing exploration into potential gastrointestinal implications of the disorder. The review synthesizes existing literature on HHT-associated gastrointestinal complications, highlighting the diverse spectrum of vascular malformations. While bleeding and iron deficiency anaemia are well-documented, this review advocates for a broader understanding of gastrointestinal involvement.

Our case study centres on a patient with a history of recurrent epistaxis and iron deficiency anaemia (IDA) who, upon presentation, exhibited clinical features indicative of Protein Losing Enteropathy (PLE). This prompted a comprehensive investigative approach, which ruled out the common aetiologies associated with PLE. Notably, genetic screening confirming HHT shifted the diagnostic paradigm, challenging prevailing notions of HHT-related gastrointestinal complications. The review explores potential mechanistic links between HHT and PLE, incorporating insights into vascular malformations, altered hemodynamic and genetic factors. By presenting this unique case and challenging existing perspectives, the review advocates for increased awareness of PLE in HHT. Recognizing this association holds significant implications for timely diagnosis and comprehensive management. The shift in perspective prompted by this review encourages further research into the intricate interplay between HHT and gastrointestinal manifestations particularly PLE, potentially reshaping clinical practice.

Keywords
Hereditary Haemorrhagic Telangiectasia (HHT), Protein Losing Enteropathy (PLE), Osler-Weber-Rendu syndrome, vascular malformations, gastrointestinal complications.

Introduction
Hereditary Haemorrhagic Telangiectasia (HHT), also known as Osler-Weber-Rendu syndrome, is a rare genetic disorder characterized by abnormal blood vessel formation. While mucocutaneous telangiectasis and arteriovenous malformations are hallmark features of HHT, there is a growing recognition of its diverse systemic manifestations. This review is motivated by the need to comprehensively understand the relationship between HHT and Protein Losing Enteropathy (PLE), a condition characterized by excessive protein loss through the gastrointestinal tract.

Our primary objectives involve conducting a thorough investigation of the existing literature on Hereditary Haemorrhagic Telangiectasia, with a specific focus on its clinical presentation, particularly gastrointestinal complications, pathogenesis, and diagnostic modalities. Within this review, we intend to thoroughly investigate Protein Losing Enteropathy and its potential connections with HHT. Our analysis will encompass diverse aspects, including the manifestations of PLE, its clinical features, and diagnostic approaches. Furthermore, we aim to investigate potential links between HHT and PLE, exploring possible mechanisms and connections between these two conditions. This examination will contribute to a deeper understanding of how HHT may be associated with protein-losing enteropathy. Moreover, the inclusion of a unique clinical case presenting with HHT and manifesting as PLE adds a distinctive clinical perspective to the current understanding of this rare association. In exploring the potential mechanisms linking HHT to PLE, we seek to unravel the underlying factors contributing to gastrointestinal manifestations in HHT patients. Finally, by identifying existing knowledge gaps, we aspire to propose future research directions that will contribute to a more nuanced comprehension of the spectrum of gastrointestinal complications in HHT. Through these objectives, our review aims to provide clinicians with valuable insights for enhanced diagnosis and management of patients presenting with PLE in the context of HHT.

Case Presentation
A 23-year-old female, previously in good health, presented with a six-week history of escalating abdominal distension and dyspnoea. Notably, she had experienced recurrent nosebleeds since the age of 18 and had a persistent iron deficiency attributed to menorrhagia. The patient, originally from Iran, had migrated to Australia in 2019 with her husband and three children. She had an uneventful obstetric history, delivering three healthy children vaginally. Her vaccination status was current, including COVID vaccination. The patient was a non-smoker, abstained from alcohol, and denied any illicit drug use. The family history indicated that both her father and grandfather had succumbed to haemorrhagic stroke at the ages of 63 and 64, respectively.

Clinical Findings
Upon clinical evaluation, multiple telangiectasias were evident on the tongue, lips, nose, and palms. The patient's blood pressure was normotensive at 120/70, with no postural hypotension. Pulse was regular at 70 beats per minute, exhibiting good volume and symmetry on both sides. Oxygen saturation measured 96% on room air. Systemic examination revealed right-sided pleural effusion with ascites. In further detail, the cardiac examination showed normal two heart sounds with a high-flow murmur over the precordium, and there were no carotid bruits. Jugular venous pressure was not elevated. Respiratory examination was consistent with right pleural effusion, as indicated by increased chest dullness, decreased vocal resonance, and bronchial breathing heard just at the top of the effusion suggestive of Ewart sign. Abdominal examination revealed ascites, as confirmed by shifting dullness, with no signs of chronic liver disease, and no bruit was heard on auscultation of the abdomen. Gross neurological examination was unremarkable, and lower limb examination showed no evidence of peripheral vascular disease.

Investigations
Initial laboratory investigations revealed iron deficiency anaemia and hypoalbuminemia

- Full blood count and iron study was notable for iron deficiency.
- Liver function tests including Alkaline phosphatase (ALP)/ Gamma-glutamyl transferase (GGT)/

Alanine transaminase (ALT)/ Aspartate aminotransferase (AST)/ Bilirubin, were within normal limits, except for a low serum total protein of 3g/dL (Reference value: 6-8g/dL) and a low serum albumin of 2g/dL (Reference value: 3-5g/dL).

- The coagulation profile, Electrocardiogram (ECG), and chest X-ray were unremarkable, except for right pleural effusion on imaging.
- Abdominal ultrasound demonstrated mild ascites, normal liver parenchyma, and no splenomegaly. Renal function tests, serum B12/Folate/Lipid profiles/Hb (Haemoglobin)A1c, and thyroid function tests were normal.

Subsequently, the patient underwent further investigations:

- Serum immunoglobulins revealed hypogammaglobulinemia: Immunoglobulin G (IgG) -0.9g/L (Reference: 7-16 g/L), Immunoglobulin A (IgA) -0.2g/L (Reference: 0.7-4g/L), and Immunoglobulin M (IgM) -0.1g/L (Reference: 0.4-2.3 g/L).
- Coeliac serology and tumour markers [Alpha fetoprotein (AFP)/Carbohydrate Antigen (CA) 19-9/Cancer Antigen (CA) 125/ carcinoembryonic antigen (CEA)] were negative.
- Faecal studies [calprotectin, occult blood, fat, microscopy and culture (MCS), Ova, cyst, parasites] were negative. Faecal elastase was 600ug/g (>500ug/g), and the faecal osmolar gap was 80Osm/kg (50-100 Osm/kg).
- Urine microscopy was negative for infection, and the urinary albumin creatinine ratio was within the normal range.
- C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) were normal.

- Diagnostic thoracocentesis confirmed transudate pleural effusion, with cytology negative for malignancy.
- Diagnostic abdominal paracentesis ruled out infection and malignancy, revealing low ascitic fluid protein and albumin with a Serum Ascitic Albumin gradient of less than 1.1g/dL.
- Transthoracic echocardiogram showed normal heart chambers, valves anatomy, ejection fraction, and no pericardial effusion.
- Human Immunodeficiency Virus (HIV), Epstein Barr Virus (EBV) and Cytomegalovirus (CMV) serology were negative.
- Further tests to screen for malignancy included Computed Tomography (CT) chest/abdomen/pelvis, myeloma screen, flow cytometry, and fasting gastrin, all of which were unremarkable.
- Gastrointestinal endoscopic examinations, encompassing gastroscopy, colonoscopy, push enteroscopy, and PillCam studies, yielded essentially unremarkable findings. No gastrointestinal pathology contributing to iron deficiency anaemia was identified. Additionally, these examinations effectively excluded the presence of other pathologies, including but not limited to inflammatory bowel diseases, gastrointestinal malignancy, coeliac disease, Whipple's disease, Menetrier's disease, and intestinal lymphangiectasia.

After excluding common causes of hypoalbuminemia and hypogammaglobulinemia, further testing for protein-losing enteropathy was pursued. Alpha-1 antitrypsin levels in the stool were elevated at 300mg/g (<2.6mg/g), and alpha-1 antitrypsin intestinal clearance was increased at 320ml/24 hours (<26ml/24 hours). Consequently, a diagnosis of Protein Losing Enteropathy was established. Given the clinical presentation characterized by recurrent spontaneous epistaxis and multiple telangiectasias, suggestive of Hereditary Haemorrhagic Telangiectasia, the patient consented to genetic testing. The results were affirmative for a mutation in the Endoglin (ENG) gene, confirming the diagnosis of hereditary haemorrhagic telangiectasia type 1.

Management

The patient was treated with diuretics, iron infusion, and dietary adjustments, including guidance on a diet rich in protein and low in fat. Additionally, she received off-label Bevacizumab at a dose of 5mg/kg fortnightly infusion for a total of 6 doses, with successful resolution of symptoms. The patient was closely monitored by a multidisciplinary team, including gastroenterologists, haematologists, immunologists, and a general physician with expertise in HHT.

Outcome

Following Bevacizumab treatment, the patient exhibited marked improvement. Symptoms such as fatigue and shortness of breath resolved, and ascites and pleural effusion disappeared. Repeat blood testing, including iron, protein, albumin, and alpha-1 antitrypsin in the stool, returned to normal levels.

Overview of HHT

Hereditary haemorrhagic telangiectasia (HHT), or Osler-Weber-Rendu syndrome, is an autosomal dominant vascular disorder characterized by epistaxis, gastrointestinal bleeding, iron deficiency anaemia, and mucocutaneous telangiectasia.

Epidemiology

Hereditary Haemorrhagic Telangiectasia is a rare genetic disorder with an estimated prevalence of 1 in 5,000 [1]. The global incidence of HHT, however, is marked by notable regional variations [2], providing a nuanced perspective on its epidemiology.

In the Afro-Caribbean population of the Netherlands Antilles, HHT presents with an incidence of 1 in 1,331, underlining the distinct prevalence patterns within specific ethnic groups. Similarly, in the Haut Jura region of France, the incidence is reported as 1 in 2,351, reflecting geographical disparities in the manifestation of this condition. Moving to the Asian continent, the Akita prefecture in northern Japan demonstrates a variable incidence, ranging from 1 in 5,000 to 1 in 8,000. This variability across regions emphasizes the complex interplay of genetic and environmental factors contributing to the epidemiology of HHT. Denmark, too, provides intriguing insights into the prevalence of HHT. Fyn County reports an incidence ranging from 1 in 1,641 to 1 in 7,246, further highlighting the diverse epidemiological landscape of HHT even within a single country.

In summary, the epidemiology of Hereditary Haemorrhagic Telangiectasia is characterized by its rarity on a global scale, with notable regional differences that underscore the intricate interplay of genetic and environmental influences in shaping the prevalence of this disorder.

Pathophysiology

Genetics and Cellular changes

Hereditary haemorrhagic telangiectasia is inherited as an autosomal dominant trait with variable penetrance and expression. Multiple genes, particularly Endoglin (ENG) in HHT1, Activin receptor-like kinase 1 (ACVRL1) in HHT2, and Suppressor of Mothers against Decapentaplegic homolog 4 (SMAD4) in Juvenile Polyposis/HHT syndrome (JPHT), contribute to HHT [3,4] with ENG and ACVRL1 accounting for the majority of reported pathogenic variants. Recently, rare instances of HHT have been linked to pathogenic variants in growth differentiation factor 2 (GDF2) [5-7], encoding the Anti-human Activin Receptor-like Kinase 1 (ALK1)/endoglin ligand bone morphogenetic protein (BMP)-9. This gene was previously associated with HHT-like features [8,9]. These genes, including GDF2, play crucial roles in the BMP/transforming growth factor beta (TGF-beta) signalling pathway (Figure 1) [10].

TGF-β binds to RII, forming a complex that activates RI and incorporates the auxiliary receptor endoglin. Activated RI transmits signals via Smad proteins to regulate gene expression. Mutations in ALK1/RI (HHT2) and Endoglin/Co-R (HHT1) disrupt this pathway, contributing to HHT development.

R-Smad: Receptor dependent Smad; I-Smad: Inhibitory SMad; Co-Smad: collaborator Smad. Adapted from Fernandez-L et al. [10]

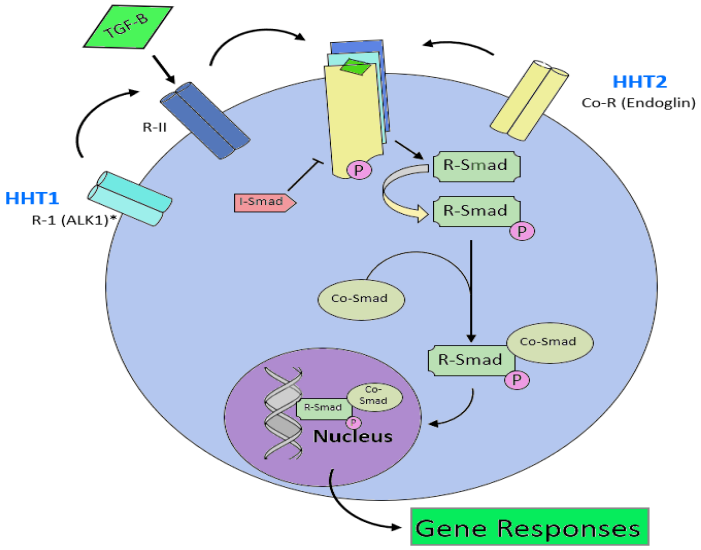

Figure 1: The TGF-β signalling pathway in the pathogenesis of HHT.

TGF-β, a signalling molecule, operates through a receptor complex involving type I (RI) and type II (RII) transmembrane serine/threonine kinase receptors. The complex may include auxiliary receptors like endoglin and beta glycan [11]. The initial binding of TGF-β to RII leads to the formation of a complex with RI and once formed, this TGF-β/RII/RI complex activates RI through phosphorylation, initiating a cascade of intracellular events involving Smad proteins [12-14]. These Smads come in three types: receptor regulated (R-Smads), common mediator (Co-Smads), and inhibitory (I-Smads). R-Smads, such as Smad1, Smad2, Smad3, Smad5, and Smad8, get activated by RI, bind to Co-Smad (Smad4), and translocate to the nucleus, activating target genes. I-Smads (Smad6 and Smad7) regulate R-Smad activity.

In hereditary haemorrhagic telangiectasia genes Smad4 and BMPRII are mutated and expressed in various cell types, including endothelial cells. In contrast, ENG and ALK1 are mainly found in the endothelium. The endothelial TGF-β system involves two types of RI—ubiquitously expressed ALK5 and endothelium-specific ALK1. Both ALK1 and ALK5 are crucial for proper TGF-β signalling in endothelial cells, but they can induce opposite responses. TGF-β/ALK1 promotes endothelial cell migration and proliferation, while TGF-β/ALK5 inhibits these effects and supports extracellular matrix deposition [15]. This duality corresponds to different phases of angiogenesis: quiescence and activation (Figure 2) [16]. The delicate balance between ALK1 and ALK5 actions in endothelial cells is a finely tuned mechanism controlled by TGF-β.

When TGF-β signals through ALK1, it stimulates proliferation and migration genes, activating angiogenesis. Conversely, dominant ALK5 signalling upregulates ECM genes while repressing proliferation and migration genes, inducing endothelial quiescence. Additionally, ALK1 and ALK5 mutually regulate each other's functions. Adapted from Lebrin et al. [16]

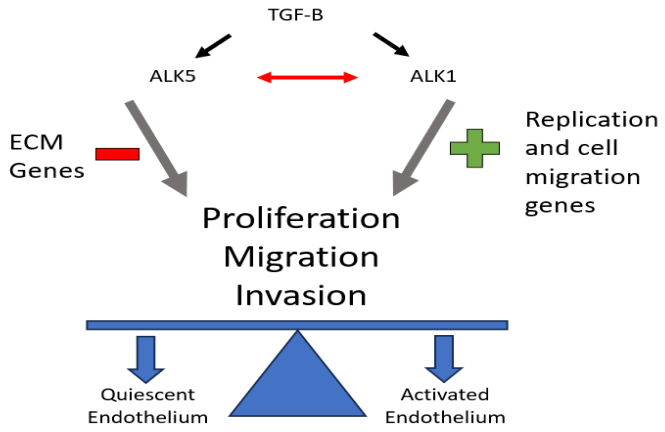

Figure 2: Equilibrium Signalling: TGF-β Receptor Balance in Endothelial Dynamics.

Types of HHT

Hereditary haemorrhagic telangiectasia (HHT) has three main types [17]

1. HHT Type I (HHT1): Caused by mutations in the ENG gene.
2. HHT Type 2 (HHT2): Results from mutations in the ACVRL1 gene, which encodes the protein activin receptor-like kinase 1 (ALK1) on chromosome 12.
3. HHT Associated with Juvenile Polyposis (JPHT): Linked to a mutation in the SMAD4 gene, which codes for the transcription factor SMAD4, a crucial downstream effector of TGF-B signalling.

The distribution of gene mutations in HHT patients is primarily ENG (61%), followed by ACVRL1 (37%), and then SMAD4 (2%). More than 600 mutations, including deletions, missense, nonsense, and insertions, have been identified in ENG or ACVR genes.

Clinical Features

1. Epistaxis

Recurrent and spontaneous nosebleeds originating from telangiectasia of the nasal mucosa are the primary clinical manifestation in HHT as 68-100% of the patient with HHT display telangiectasia on the nasal mucous membrane [18].

2. GIT manifestation of HHT

α. Gastrointestinal Bleeding

Gastrointestinal bleeding is a prevalent manifestation in individuals with HHT, occurring in 13–30% of cases and typically manifesting after the age of 50 [19]. While numerous case reports and case series document overt or obscure gastrointestinal bleeding, a dearth of specific data persists regarding the association between gastrointestinal bleeding and HHT [20,21]. Factors such as advancing age, ENG mutation, tobacco use, and low haemoglobin levels have been linked to gastrointestinal involvement in HHT patients [22].

β. Hepatic Manifestations

Hepatic manifestations in HHT include arteriovenous shunts, arterioportal shunts, and Porto venous shunts. Extensive hepatic arteriovenous shunts can lead to chronic liver ischemia, ultimately resulting in liver fibrosis and cirrhosis. The estimated prevalence of hepatic involvement in HHT ranges from 74% to 79% [23-27]. Arterioportal shunts are associated with portal hypertension and its manifestations, including abdominal ascites or gastrointestinal bleeding from varices. Imaging studies may reveal an enlarged portal vein, hepatic vein, and inferior vena cava, accompanied by liver structure abnormalities such as heterogeneity, nodules, and regions with abnormal parenchymal perfusion. This perfusion irregularity may hinder hepatocellular regenerative activity, leading to conditions like focal nodular hyperplasia (FNH) [28], which is markedly more prevalent in HHT patients (100 times greater) compared to the general population, or nodular regenerative hyperplasia [19-21]. Additional manifestations linked to liver involvement include heightened preload leading to high-output cardiac failure, portal hypertension, mesenteric ischemia, and biliary disease.

3. Mucocutaneous Telangiectasia

Most individuals exhibit skin and buccal mucosa telangiectasia later in life, but these may be absent or inconspicuous in younger individuals [17,29]. These manifestations predominantly appear on the lips, tongue, buccal mucosa, and fingertips.

4. AV malformations

Clinically significant arteriovenous malformations (AVMs) may present in diverse organs, with notable prevalence in vital structures such as the lungs, brain, and liver.

5. Iron Deficiency Anaemia

Epistaxis is a frequent cause of iron deficiency in HHT, while a smaller subset experiences iron deficiency anaemia from gastrointestinal bleeding. Anaemia in HHT can also be influenced by factors such as menorrhagia, intercurrent infection or inflammation hindering iron absorption, and low-grade homolysis.

6. Pulmonary HTN

Pulmonary hypertension in HHT is usually due to increased pulmonary flow due to systemic AVMs and/or anaemia [30,31]. However, it may be due to a pure pulmonary arterial hypertension (PAH) phenotype indistinguishable from PAH in the general population [31].

7. Venous Thromboembolism

Individuals with HHT face an elevated risk of venous thromboembolism (VTE). In a prospective study encompassing 609 HHT patients across two distinct series at a single centre, the heightened VTE risk was linked to low serum iron levels, primarily stemming from insufficient replacement of iron lost due to bleeding. This condition correlated with increased plasma levels of coagulation factor VIII [32].

Diagnosis

HHT can be clinically diagnosed using three or more Curaçao Criteria or by identifying a pathogenic or likely pathogenic variant in an HHT gene.

The Curaçao diagnostic criteria encompass four key findings: [1,33]

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

These criteria categorize diagnoses as "definite" (three or four criteria), "suspected" (two criteria), and "unlikely" (zero or one criterion). Genetic testing is another method for diagnosis, involving the identification of a pathogenic sequence variant in ENG, ACVRL1, SMAD4, or GDF2.

Management

The management of HHT involves targeted interventions addressing organ-specific signs and symptoms, such as epistaxis, gastrointestinal bleeding, iron deficiency, arteriovenous malformations (AVMs), and associated complications.

Epistaxis Management

The 2020 International Guideline provides a stepwise approach to epistaxis treatment, involving topical therapies, oral tranexamic acid as a second-line option, ablative therapies by otorhinolaryngologists, and systemic antiangiogenic therapy, such as bevacizumab and immunomodulatory imide drugs (IMiDs) like thalidomide and lenalidomide [34-43]. Although there is a lack of randomized controlled trials for IMiDs in HHT, a systematic review in 2018 suggested a potential association between low-dose thalidomide use and reduced epistaxis frequency and duration [44]. Additionally, non-guideline approaches such as tamoxifen, raloxifene, phosphoinositide 3-kinase inhibitors, mammalian target of rapamycin (mTOR) inhibitors, septal dermatoplasty, and Young's procedure have been explored, with varying degrees of evidence supporting their efficacy [45-47].

A notable addition to the armamentarium is Pazopanib, an orally administered tyrosine kinase inhibitor that blocks vascular endothelial growth factor (VEGF) receptors, potentially serving as anti-angiogenic treatment for hereditary haemorrhagic telangiectasia. A discernible improvement in haemoglobin levels and/or reduction in epistaxis occurrences was observed in all patients treated with Pazopanib [48].

Gastrointestinal Bleeding

Local endoscopic therapy, utilizing argon plasma coagulation or neodymium-doped yttrium, aluminium, and garnet laser, may be employed to reduce HHT-related gastrointestinal bleeding [1,4].

There are limited case series and case reports available on systemic approaches to managing gastrointestinal bleeding associated with Hereditary Haemorrhagic Telangiectasia. Early studies and

clinical experiences initially suggested the efficacy of hormonal therapy [49-52]. However, more recent research indicates a more favourable benefit-risk ratio for antifibrinolytics [53] and anti-angiogenic therapies, including bevacizumab [35-37,48], and thalidomide [54,55]. Tranexamic acid may offer some utility for mild to moderate GI bleeding, although its impact is likely modest. Studies have demonstrated improved nasal bleeding, but no significant enhancement in anaemia [53]. In patients with moderate to severe bleeding, particularly those dependent on transfusions or intravenous (IV) iron, IV bevacizumab has shown a significant reduction in transfusion requirements in several uncontrolled case series, demonstrating a good safety profile [35-37]. Recurrence of GI bleeding following the initial response to IV bevacizumab "induction" therapy is common, and may require maintenance dosing. However, the potential long-term benefits and the optimal treatment regimen are yet to be defined. Additional anti-angiogenic drugs such as pazopanib, pomalidomide, doxycycline, and specific estrogen receptor modulators (SERMs) like tamoxifen, raloxifene, or bazedoxifene, may be considered as potential agents [56-58]. Nevertheless, evidence supporting their efficacy in HHT-related GI bleeding remains limited and is primarily based on small case numbers. Iron deficiency and anaemia secondary to vascular lesions are managed conservatively by repletion of lost iron.

Hepatic AVMs

The international consensus recommends screening all HHT patients for hepatic AVMs, with treatment reserved for symptomatic cases [59]. Severe cases unresponsive to therapy may explore options such as bevacizumab [38,41] or liver transplantation [60,61]

Pulmonary Venous Malformations (PAVMs)

Prophylactic antibiotics are recommended for patients with PAVMs before procedures causing bacteraemia [62]. Embolotherapy is advised for amenable PAVMs [63-67], while surgical intervention or lung transplantation may be considered in specific cases.

Cerebral Arteriovenous Malformations

Treatment is recommended for cerebral or spinal vascular malformations larger than 1 mm, involving options such as embolization, microsurgical obliteration, stereotactic radiation, or a combination thereof. Lesions not requiring immediate treatment should undergo regular follow-up with magnetic resonance imaging and cerebral angiography [1,4]. While expert opinion guides current practices, a paucity of randomized controlled trials exists for various therapeutic modalities in HHT [1]. The use of systemic bevacizumab presents a promising therapeutic avenue for HHT. According to the second International HHT Guideline, uncontrolled retrospective series have demonstrated that intravenous bevacizumab can mitigate epistaxis, improve anaemia, reduce transfusion requirements, and enhance overall quality of life [34-43]. A multicentre retrospective study in 2021 further supported the favourable safety and efficacy profiles of systemic bevacizumab in a cohort of 238 individuals with HHT [68]. The intricate nature of HHT necessitates a multifaceted approach, involving input from specialists in gastroenterology, hematology, immunology, and general medicine.

Protein Losing Enteropathy

Protein-losing enteropathy (PLE) is a complex syndrome associated with excessive protein loss in the gastrointestinal tract, resulting in hypoalbuminemia, a phenomenon attributed to diverse etiological factors. This pathology should be considered in individuals exhibiting diminished serum protein levels, particularly after the exclusion of alternative causes contributing to hypoproteinemia. It is not a singular ailment but rather an unconventional presentation associated with other medical conditions [69].

The pathophysiology of protein-losing enteropathy encompasses diverse mechanisms, including lymphatic obstruction (Figure 4) [70], which may result from primary intestinal lymphangiectasia, right-sided heart failure, constrictive pericarditis, congenital heart disease, Fontan procedure for single ventricle, cirrhosis with portal hypertension gastropathy, hepatic venous outflow obstruction, mesenteric tuberculosis or sarcoidosis, retroperitoneal fibrosis, lymphoenteric fistula, lymphoma, and thoracic duct obstruction [71-73]. Additionally, mucosal diseases contribute to PLE, involving inflammatory bowel diseases, gastrointestinal malignancies, stomach or duodenal erosions or ulcers, Clostridium difficile colitis, carcinoid syndrome, and graft vs. host disease (Figure 5) [70]. Furthermore, increased mucosal permeability is associated with conditions such as tropical sprue, celiac disease, Menetrier disease, amyloidosis, cutaneous burns, eosinophilic gastroenteritis, bacterial overgrowth, intestinal parasitic infections, Whipple disease, collagenous colitis, AIDS, mixed connective tissue diseases, systemic lupus erythematosus (SLE), and rheumatoid arthritis (RA) (Figure 6) [70,74,75].

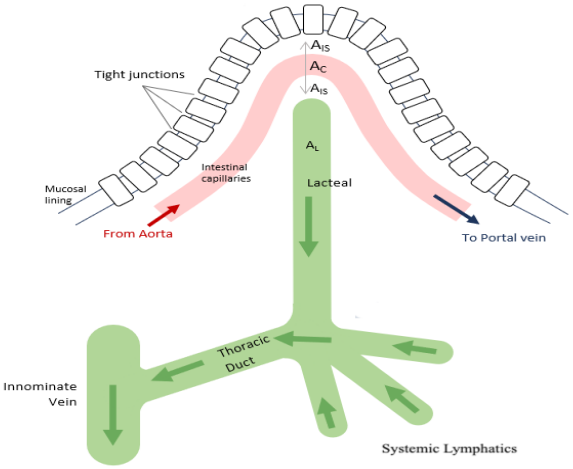

Figure 3: Normal Intestinal Mucosa. A_{is} - Albumin in interstitial Space; A_c - Albumin in Intestinal Capillaries Plasma; A_L – Albumin in Lymphatics.

Epithelial cells form a barrier between the interstitial space and lumen. Albumin slowly leaks from the intestinal capillaries plasma to the interstitial space and the lymphatics eliminate interstitial albumin leaked from plasma to venous system via thoracic duct. Adapted from David et al. [70]

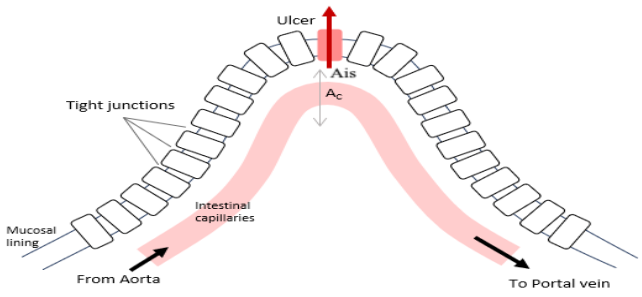

Figure 4: PLE due to elevated Lymphatic Pressure resulting from increased venous pressure.

Elevated central venous pressure disrupts Starling forces, increasing capillary filtration and lymph production in the gut mucosa. Rupture of lymphatics in the intestinal tract exacerbates this imbalance, reducing plasma albumin and oncotic pressure. Additionally, elevated pressure in the innominate vein increases resistance to thoracic duct drainage, further worsening lymphatic dysfunction and PLE [70].

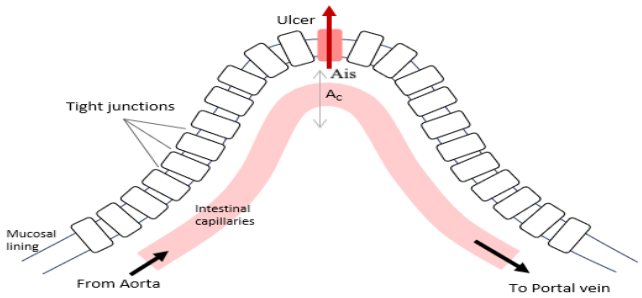

Figure 5: PLE secondary to mucosal disease.

The intestinal mucosal erosions cause the breakdown of the mucosal barrier allowing unrestricted movement of interstitial protein into the intestine resulting in PLE [70].

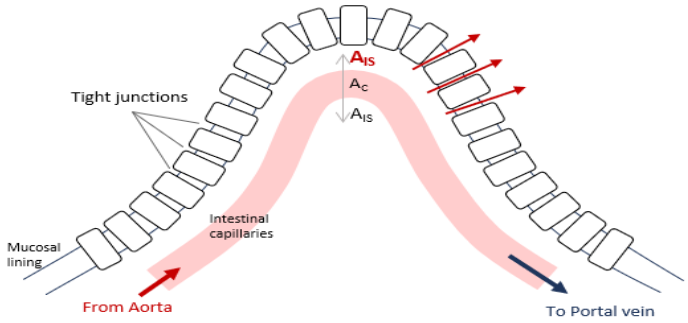

Figure 6: PLE resulting from increased intestinal mucosal permeability.

It is hypothesized that increased mucosal permeability results from dysfunction in the epithelial tight junctions [70] resulting in PLE. Protein-losing enteropathy (PLE) presents with diverse clinical manifestations, primarily dictated by its underlying causes. Patients commonly exhibit peripheral oedema, failure to thrive, frequent infections, and, occasionally, sepsis due to chronic hypogammaglobulinemia while some may experience gradual dyspnoea or painless abdominal distention due to pleural/pericardial effusions or ascites. Chylothorax or chylous ascites may occur in systemic diseases or widespread lymphatic malformations. Hypogammaglobulinemia and lymphocytopenia vary among PLE patients, and their impact on immune function is not clearly understood, with inconsistent observations in opportunistic infections [76] and a lack of typical diseases associated with lymphocytopenia even in patients with low Clusters of differentiation 4+ (CD4+) counts [77].

The most common test performed to diagnose PLE is Alpha 1 antitrypsin (A1AT) intestinal clearance. It is calculated as-
Alpha 1-antitrypsin clearance = (stool volume) x (stool alpha 1-antitrypsin)/ (serum alpha-1 antitrypsin).
Alpha-1 antitrypsin is a glycoprotein synthesized in the hepatic tissue and is a principal constituent of the alpha-1 globulins and has molecular weight greater than albumin. Due to its resistance to proteolysis and degradation within the intestinal lumen, it is excreted intact in faecal matter [78,79]. Elevated clearance of alpha-1 antitrypsin serves as a diagnostic indicator for protein losing enteropathy.

Additional diagnostic assessments such as the gold standard 51Cr-labeled albumin clearance, and technetium 99 labelled serum albumin scintigraphy, may be conducted when there is a strong clinical suspicion of protein-losing enteropathy (PLE) despite a negative result in the Alpha 1 antitrypsin (A1AT) clearance test. While these tests demonstrate high sensitivity, it is noteworthy that they are intricate, costly, and not ubiquitously accessible, thus precluding routine implementation [80].

Management strategies for PLE

The management approach for protein-losing gastroenteropathy (PLE) involves addressing nutritional deficiencies through dietary interventions and treating the underlying medical condition and its symptomatic manifestations. A key component of this strategy is the adoption of a low-fat, high-protein regimen with a focus on medium-chain triglycerides. This dietary approach has demonstrated positive effects on hypoalbuminemia, gastrointestinal symptoms, and growth outcomes [81-83].

Treatment of Underlying Condition

The cornerstone of PLE management lies in addressing the root cause of protein-losing enteropathy. This involves a meticulous examination and targeted intervention to mitigate the factors contributing to the condition, forming the foundation for effective management.

Short-Term Albumin Infusion

To elevate plasma oncotic pressure and manage the immediate consequences of PLE, short-term albumin infusion is employed. This intervention is designed to address the acute effects of protein loss and stabilize the patient's condition.

Nutritional Monitoring and Support

A crucial component of PLE management involves meticulous nutritional monitoring and support. This includes the careful assessment and correction of malnutrition or micronutrient deficiencies, if present. A high-protein diet is generally recommended, with a target range of 2-3 g/kg/day of protein intake. This nutritional approach aims to replenish lost proteins and support overall health.

Supportive Care for Oedema

Managing oedema associated with PLE requires a multifaceted approach. Supportive measures, such as the use of support stockings, limb elevation, and vigilant monitoring for skin breakdown, are implemented to address and alleviate oedematous symptoms [84,85]. Additionally, promoting adequate ambulation is emphasized to prevent complications such as deep vein thrombosis, contributing to a holistic strategy for oedema management. In addition to the aforementioned strategies, the management of Protein Losing Enteropathy (PLE) often involves the judicious use of medications to alleviate specific symptoms associated with the condition. Diuretics, such as furosemide or spironolactone, are commonly employed to manage fluid retention and reduce oedema, contributing to an overall improvement in patient comfort. Sildenafil, a selective pulmonary vasodilator, may be prescribed to address vascular complications and enhance blood flow in specific cases. Steroids, including prednisone or budesonide, are utilized to modulate the immune response and mitigate inflammation, which can play a role in the manifestation of PLE. These medications aim to suppress the inflammatory processes contributing to protein loss and symptom exacerbation. Octreotide, a somatostatin analogue, may be recommended to manage PLE symptoms by inhibiting the release of various hormones and reducing intestinal blood flow. This can contribute to a decrease in protein loss and amelioration of gastrointestinal symptoms associated with PLE.

In summary, the management of Protein Losing Enteropathy (PLE) entails a comprehensive approach with pharmacological interventions, including diuretics, selective pulmonary vasodilators, steroids, and somatostatin analogues. These medications are carefully selected to address specific symptoms and the underlying mechanisms contributing to protein loss. Simultaneously, the holistic management strategy involves treating the root cause, implementing short-term interventions for immediate relief, and incorporating comprehensive measures for nutritional support and oedema management. This multifaceted approach aims to optimize patient outcomes and enhance the overall quality of life for individuals affected by PLE.

In our patient, the clinical presentation included abdominal distension, ascites, and pleural effusion, indicative of significant protein loss. The investigation revealed elevated alpha-1 antitrypsin in the stool with increased alpha-1 antitrypsin clearance confirming the diagnosis of PLE. She responded well with Dietary intervention/ diuretics/Iron infusion and trial of Bevacizumab for HHT. Notably, a trial of Bevacizumab for HHT resulted in a favourable resolution of PLE symptoms. This observed improvement with Bevacizumab underscores the potential association between PLE and HHT, emphasizing the latter as a plausible manifestation of the former.

Discussion

The discussion delves into potential mechanisms linking HHT to PLE. Our patient's initial presentation with PLE led to the discovery of HHT, highlighting the diverse clinical spectrum of this disorder. This case serves as a catalyst for exploring new avenues in understanding HHT-related GIT complications, with a particular emphasis on PLE. Recognizing this association is crucial for timely diagnosis and comprehensive patient care.

Mechanism of PLE in HHT

While no documented cases of Protein Losing Enteropathy in the context of Hereditary Haemorrhagic Telangiectasia have been reported, we can speculate on potential mechanisms that might underlie the connection between these two conditions. Though empirical evidence linking PLE and HHT is limited, several plausible pathways merit consideration:

a. Increased Permeability

Vascular malformations may result in increased permeability of blood vessels in the gastrointestinal tract. This heightened permeability allows proteins to leak into the intestinal lumen, leading to their loss in the faeces.

In the study 'Vascular defects associated with hereditary haemorrhagic telangiectasia revealed in patient-derived isogenic iPSCs in 3D vessels on chip,' [86] researchers developed an in vitro model using human-induced pluripotent stem cells (hiPSCs) to investigate vascular abnormalities in Hereditary Haemorrhagic Telangiectasia, particularly HHT1 with ENG gene mutations. The findings demonstrated poor endothelial cell (EC)-pericyte interaction and the formation of a leaky 3D vascular network, suggesting a link between HHT and increased vascular permeability. Notably, differences in vessel formation and reduced junctional localization of ZO1(zonula occludens-1) were observed, indicating alterations in vascular integrity. The study provides evidence supporting the association of HHT, specifically HHT1, with vascular instability and increased permeability.

b. Defect in the Intestinal Tight Junctions

While no documented evidence or specific studies have directly investigated the impact of HHT on intestinal tight junctions, the observed defect in ZO1, a tight junction protein, in the endothelium [86] raises intriguing possibilities. Given the critical role of tight junctions in maintaining the integrity of the intestinal epithelium, it is conceivable that disruptions in ZO1 or other tight junction proteins in the intestinal epithelium could potentially contribute to conditions like Protein-Losing Enteropathy. Further research

exploring the relationship between HHT, tight junctions in the intestinal epithelium, and PLE may unveil important connections in the pathophysiology of this genetic disorder.

c. Gastrointestinal Telangiectasia

Gastrointestinal Telangiectasia may instigate the onset of Protein-Losing Enteropathy through various possible mechanisms. Altered hemodynamic within the vascular bed represents a potential pathway, exerting shear stress on vessel walls and consequently eliciting mucosal inflammation, damage, and the subsequent occurrence of protein leakage. Moreover, alteration in the coagulation and fibrinolysis cascades [87] in individuals with HHT may contribute to ischemic events and bleeding within the gastrointestinal tract. Elevated levels of factor VIII and von Willebrand factor in HHT patients indicate an augmented predisposition to venous thrombosis [88-90]. Additionally, the involvement of sol-eng in HHT is noteworthy; as it facilitates platelet adhesion through the IIb3 integrin complex [34], this mechanism may elucidate the tendency of HHT patients to experience prolonged and profuse bleeding. Cumulative instances of recurrent bleeding or mucosal ischemia can perpetuate mucosal injury, compromising the integrity of the gastrointestinal lining and substantively contributing to the phenomenon of protein leakage observed in PLE. When examining these potential mechanisms, it is crucial to acknowledge the speculative nature of some hypotheses and emphasize the necessity for further research to validate these associations. The complex interplay of these mechanisms may contribute to the multifaceted nature of PLE in the context of HHT.

Conclusion

The existing literature predominantly concentrates on vascular complications in Hereditary Haemorrhagic Telangiectasia (HHT), often overlooking the potential gastrointestinal implications. Through a meticulous review of pertinent studies and the incorporation of our presented case, this study endeavours to challenge this lacuna and underscore the imperative for heightened awareness regarding Protein Losing Enteropathy (PLE) as a plausible complication of HHT. This paradigmatic shift holds the potential to significantly impact diagnostic procedures and inform more nuanced management strategies.

In summary, this review refutes the prevalent notion that PLE is not a recognized complication of HHT. The distinctive case under consideration prompts a reassessment of GIT complications in the context of HHT, urging increased vigilance in identifying PLE. Such a reframing of perspectives could exert substantial influence on clinical practices, instigating a demand for further exploration into the intricate interplay between HHT and gastrointestinal manifestations. The highlighted case serves as a poignant illustration of the critical importance of acknowledging the interrelationship between PLE and HHT. It underscores the necessity for a comprehensive understanding of these conditions to ensure accurate diagnosis and effective management. The successful implementation of Bevacizumab in our patient serves as an exemplar of the potential efficacy of targeted therapies in addressing the vascular abnormalities inherent to HHT. This calls for additional research endeavours to delve into the enduring efficacy and safety of such interventions within the purview of HHT-related complications.

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