Hereditary Hemorrhagic Telangiectasia Presenting as Severe Anemia and High Output Heart Failure: A Case Report with Literature Review

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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 5,000 people to one in every 8,000 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 [5]. 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 AVMs (50%) that can cause dyspnea, hemoptysis, paradoxical emboli, and cerebral abscesses; cerebral AVMs (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 cardiac failure and hepatic decompensation, ultimately necessitating liver transplantation [9].

Clinical diagnosis of HHT is made using the Curacao criteria, which include first-degree family history of HHT, visceral involvement, recurrent spontaneous nosebleeds, and mucocutaneous telangiectasias. If three or more criteria are met, the diagnosis is considered to be conclusive; if only two criteria are met, the diagnosis is considered to be suspected HHT [10] [Table 1]. If less than two criteria are met, the diagnosis is considered to be unlikely HHT.

Table 1 Curaçao diagnostic criteria for hereditary hemorrhagic telangiectasias

List of criteria	Number of criteria present	Likelihood of diagnosis
Recurrent spontaneous nosebleeds Mucocutaneoustelangiectasias Visceral organ involvement First-degree family history of HHT	[?] 3	Definitive
	2	Suspected
	<2	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 counselling for patients and families.

The patient's presenting symptom determines the course of treatment for HHT. Sclerotherapy, oral tranexemic acid, nasal lubrication, or surgical ablation are all options for treating epistaxis. Liver AVMs should get treated only when there is symptomatic liver failure or high output cardiac failure. 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 describe a case of definite HHT presented with severe anemia and high-output heart failure requiring frequent blood transfusions.

Case Presentation

A 42-year-old male Ethiopian patient presented to Yekatit 12 Hospital Medical College with a two-day history of worsening of shortness of breath, which followed multiple episodes of massive bilateral epistaxis. He also noted light-headedness, dizziness, tinnitus, easy fatigability, intermittent vomiting of ingested matter, generalized body swelling which started from the legs, palpitation, orthopnoea and paroxysmal nocturnal dyspnoea.

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 liter per episode. He also had passage of black tarry stools for the last 7 months which was first noticed after hospitalization. Before his current admission, he was hospitalized 3 times in the last 2 years, with diagnosis of high output heart failure secondary to severe anemia. On his last admission, he received 5 units of packed red blood cells and was also given oral iron, folic acid and proton pump inhibitors. 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.

Laboratory investigations revealed hemoglobin of 4g/dl (MCV 78fL), iron studies revealed low serum iron level of 20ug/dl (reference range: 33-193ug/dl) and low ferritin level of 16.8ng/ml (reference range: 30-150ng/ml); liver enzymes and renal function tests which were with in normal limits and normal coagulation profile. 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%. Upper GI endoscopy showed multiple telangiectatic spots in the stomach and duodenum oozing heme while colonoscopy showed pale mucosa with normal vascular architecture (Figure 2). Abdominal ultrasound with doppler study showed minimal bilateral pleural effusion and hepatic AV malformations (Figure 3).

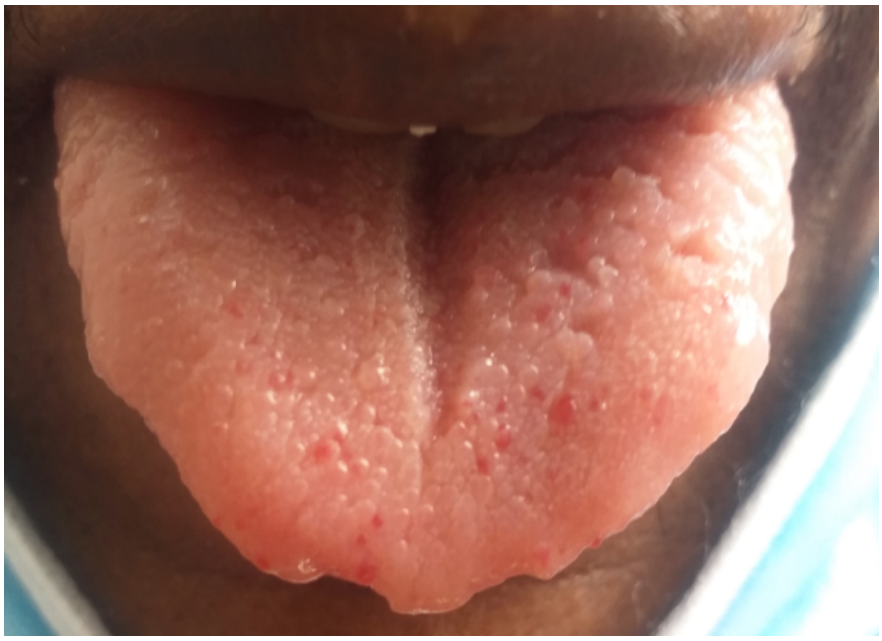
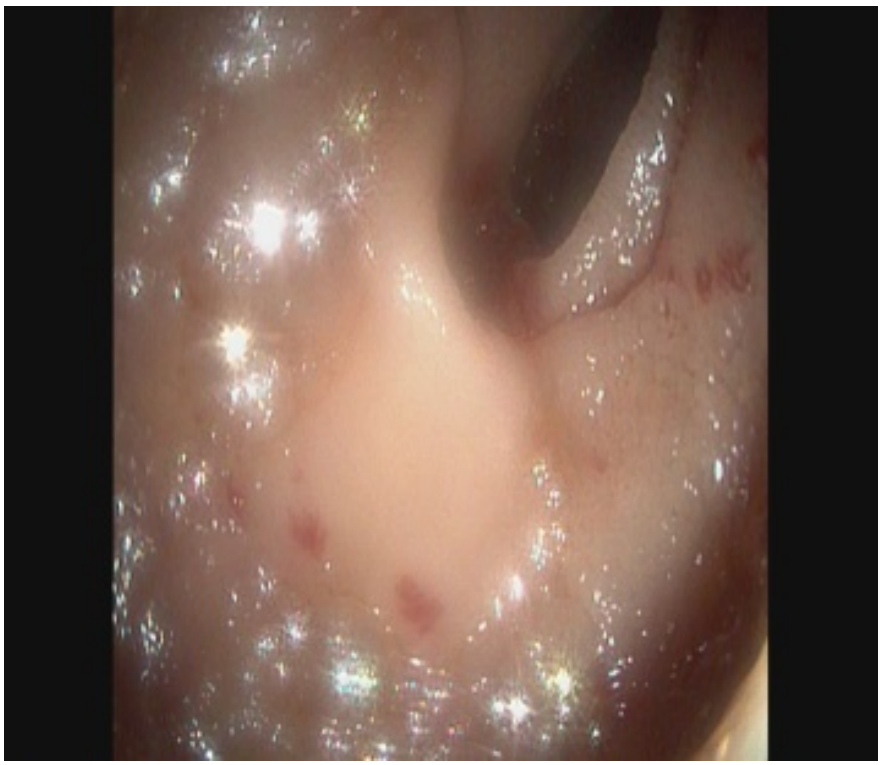
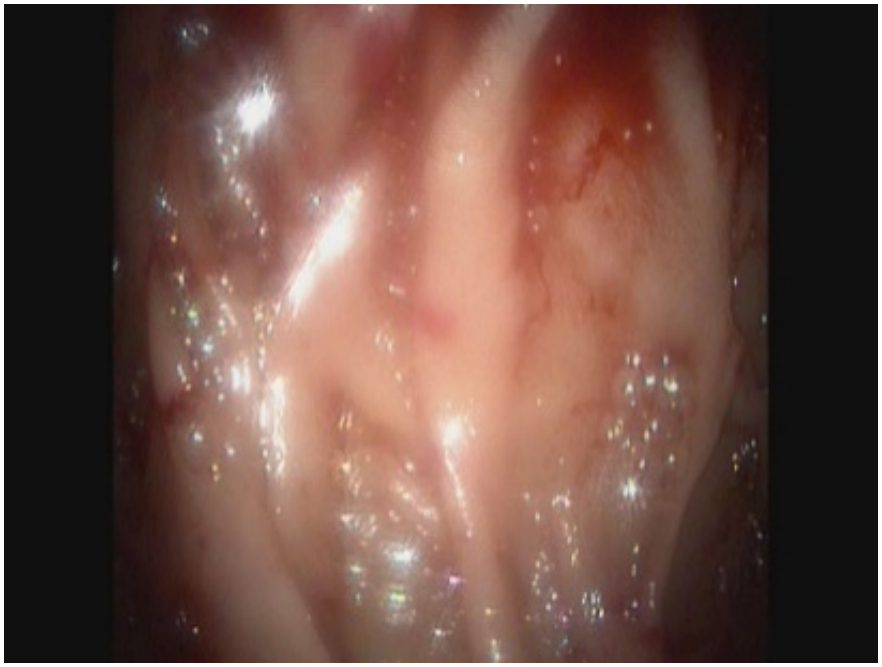
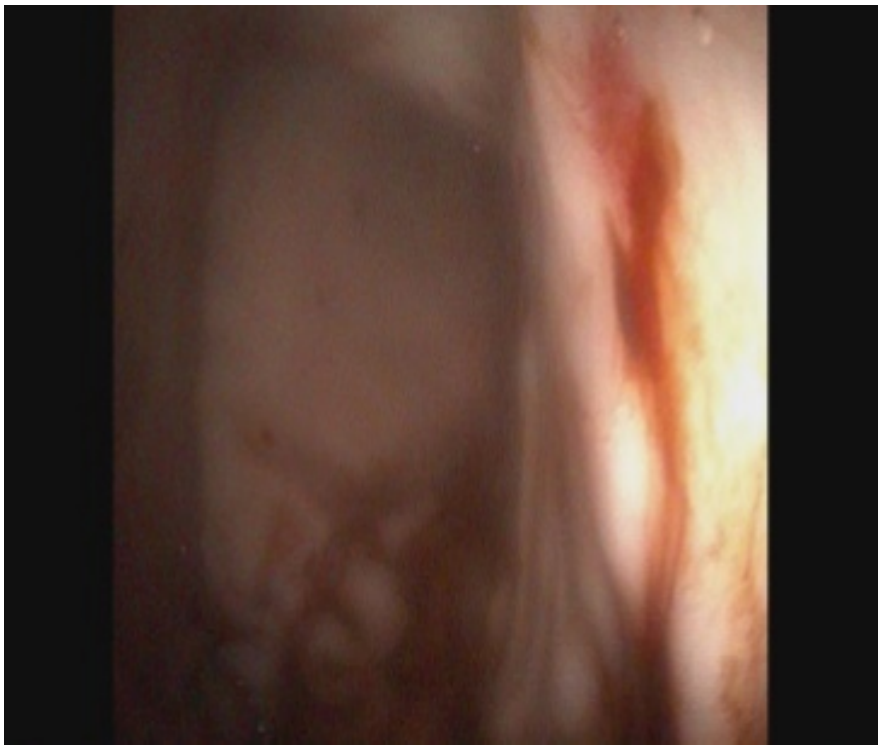
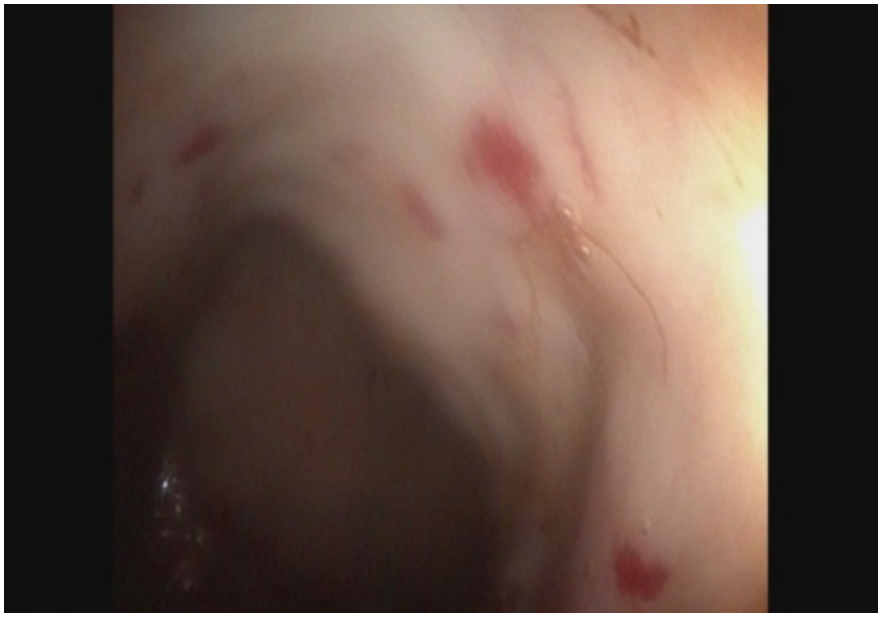


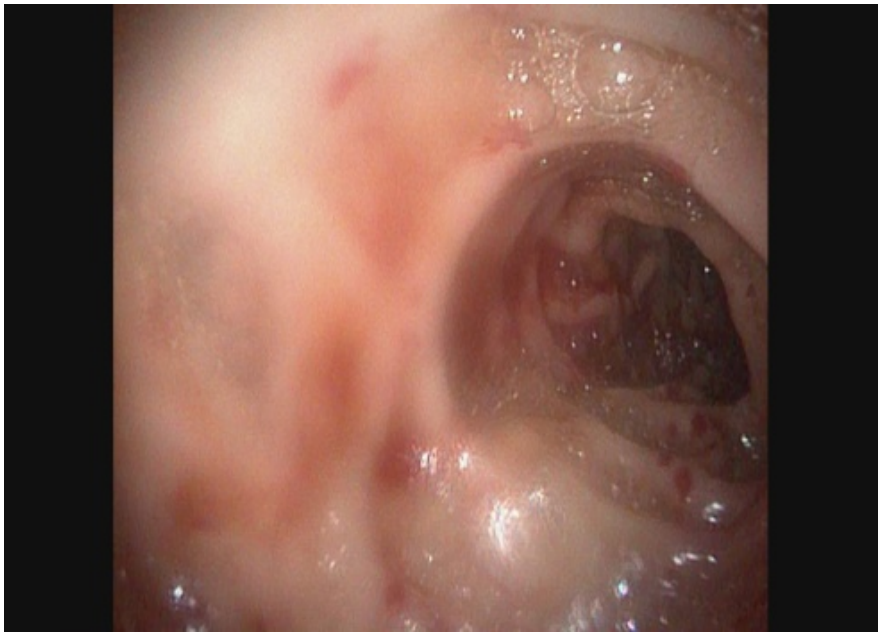
Figure 1. Multiple telengiectasias on the tongue











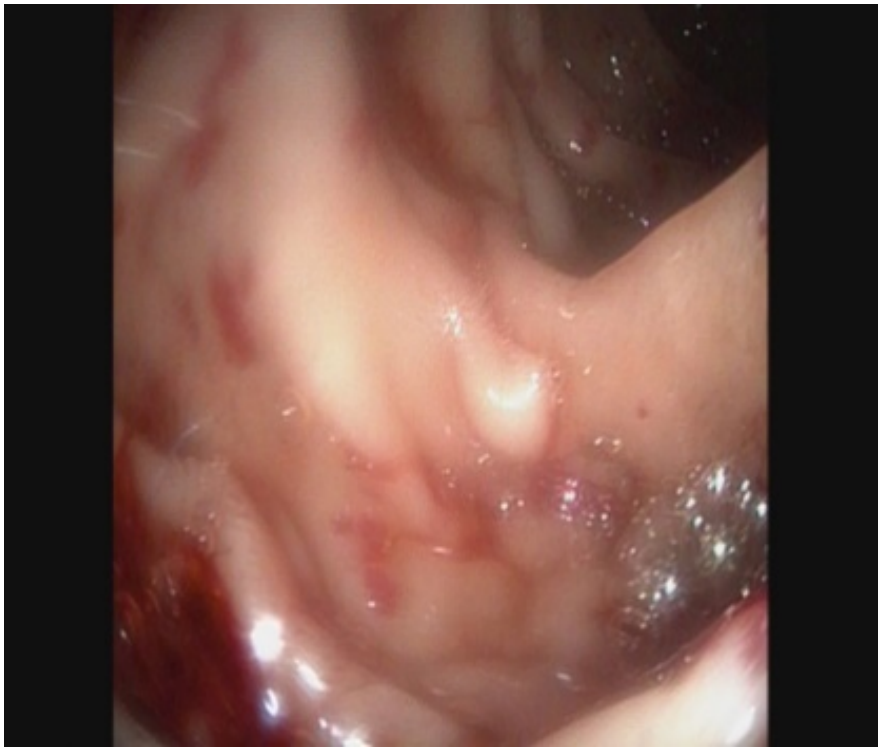
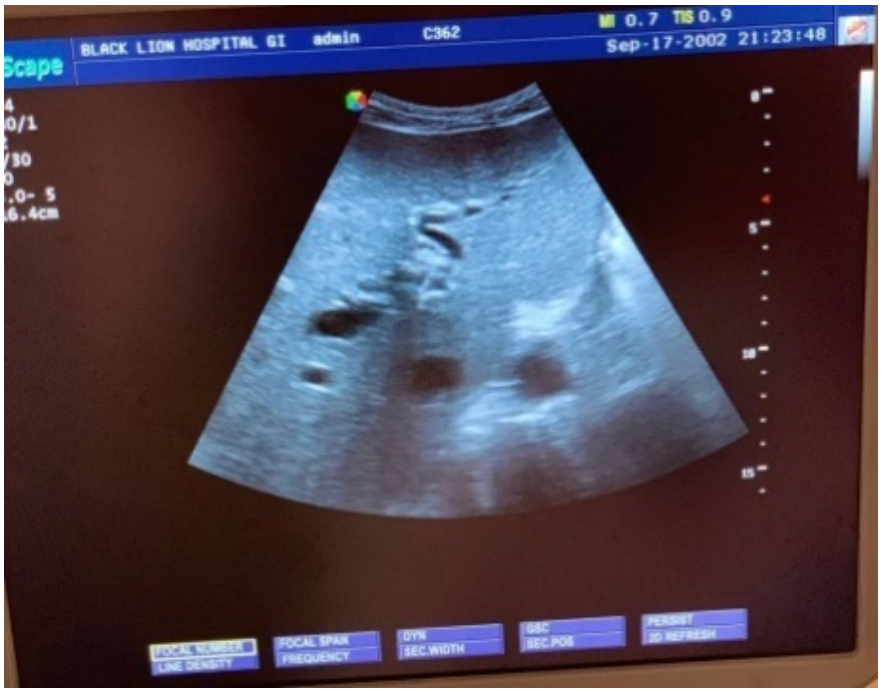
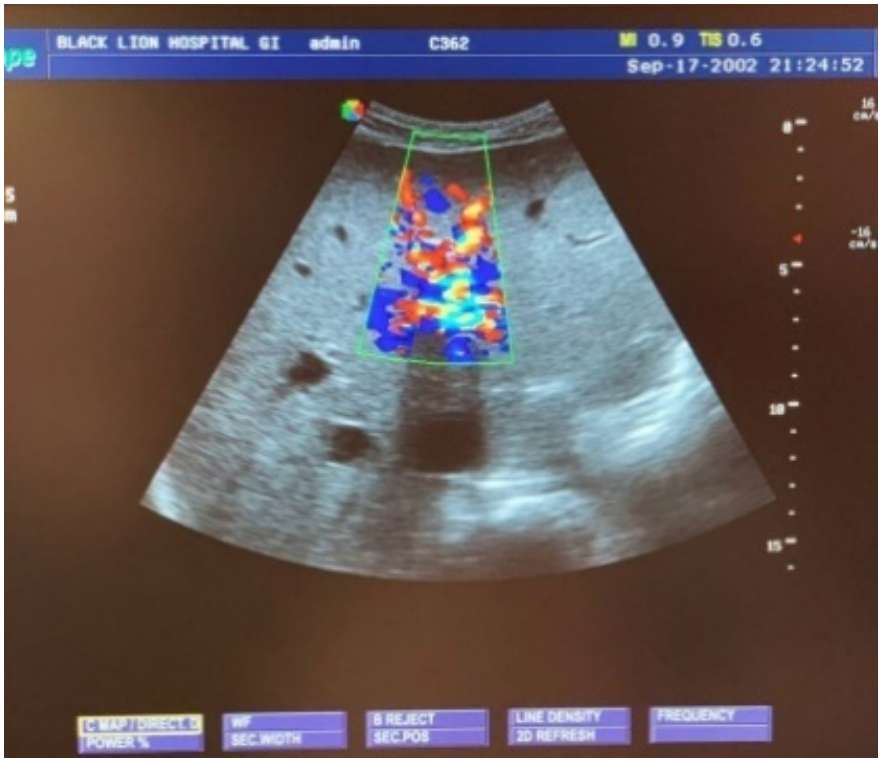


Figure 2. Upper GI endoscopy of the patient showing multiple gastroduodenal telengiectasias





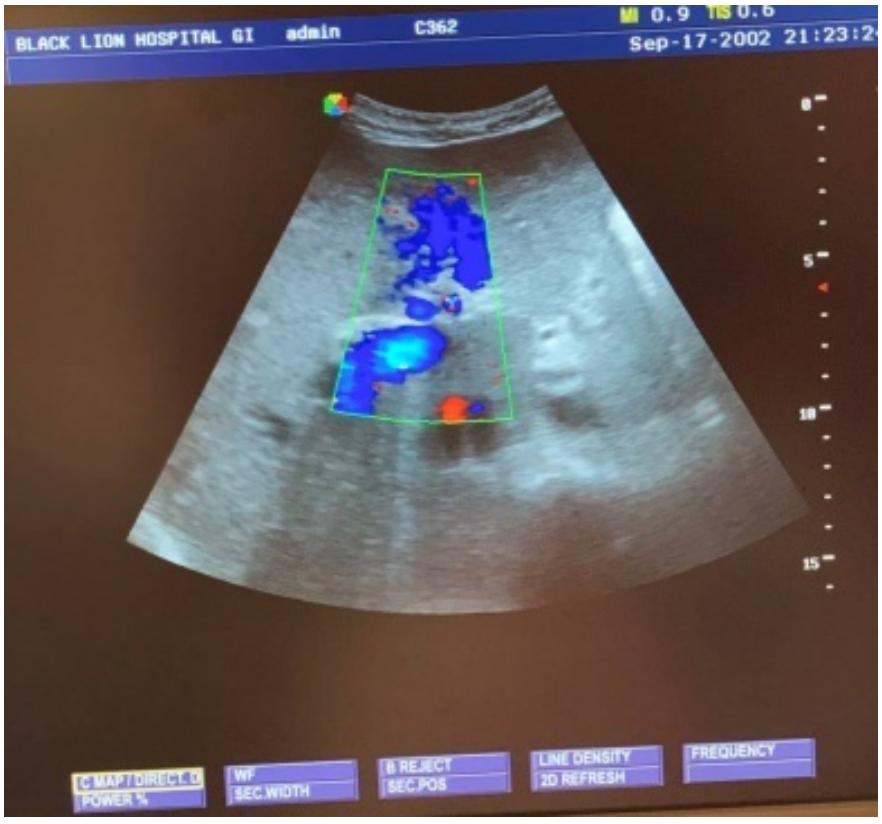


Figure 3. Hepatic AV malformation on doppler ultrasound

He was frequently hospitalized because of the severe anemia and high output heart failure; received frequent blood transfusions and put on diuretics and had nasal packing applied during episodes of nasal bleeding. 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, after which there was no drop in hemoglobin and he did not require transfusion. 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.

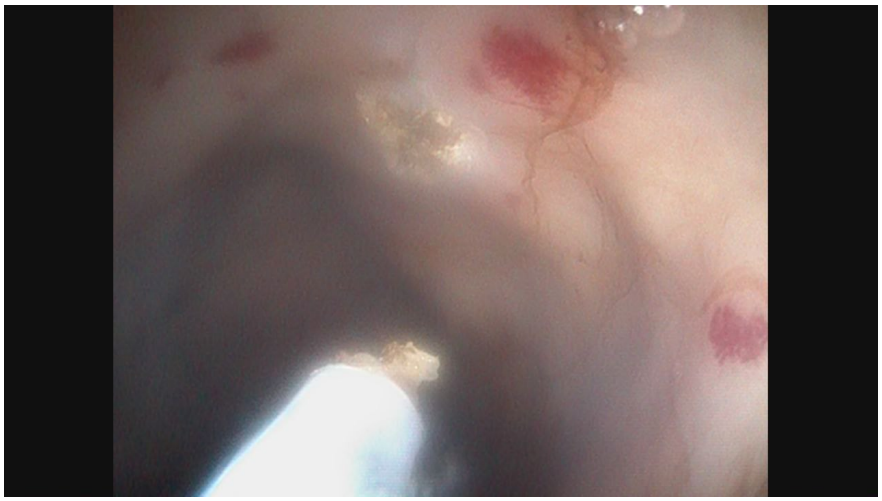


Figure 4. Endoscopic electrocauterization of telangiectasias

Discussion

Hereditary hemorrhagic telangiectasia (HHT, also known as Osler Weber Rendu syndrome) is characterized by the growth of arteriovenous malformations (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 mucocutaneoustelangiectasias are the most prevalent clinical symptoms of HHT, occurring in more than 90% of affected people by the age of 40 [15]. Our patient never noted any bleeding from his oral telangiectatic lesions. By the time a patient reaches the age of 30 [16], telangiectasias are more prevalent, infrequently bleed, and impact 70% of individuals. 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 in more than 90% of cases, epistaxis is the disease's initial clinical manifestation and that it usually happens before the age of 20 [17].

Up to 30% of patients experience recurrent gastrointestinal (GI) bleeding as a result of telangiectasias [18]. The upper GI endoscopy of our patient revealed numerous gastroduodenal telangiectasia and gastrointestinal hemorrhage. These results verified that our patient's GI telangiectasias are the sources of 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, 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 arteriovenous shunting in the liver is the most prevalent condition [23]. In our patient, liver Doppler ultrasound revealed a hepatic AV malformation, which can explain the heart failure in addition to severe anemia caused by blood loss [Figure 3].

Visceral AVMs, which are mostly asymptomatic, affect the cerebral, pulmonary, hepatic and, sporadically spinal vasculature [24]. Though abdominal ultrasound revealed signs of hepatic AVMs, our patient was not screened for pulmonary and cerebral AVMs because of financial constraints.

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 transfusion 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 [25, 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.

Conclusion

To the best of our knowledge, this is the first case of hereditary hemorrhagic telangiectasia (HHT) to be reported from Ethiopia. High degree of suspicion and early diagnosis of HHT is essential to start preventive screening and surveillance and intervene timely because of its fatal complications. Recurrent massive epistaxis and gastrointestinal hemorrhage leads to severe anemia and heart failure. In resource limited settings, selective cauterization of telangiectasia will help to control bleeding, although it does not avoid recurrent bleeding.

Ethical Clearance

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

Consent for publication

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

Funding statement

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Disclosure

We don't have conflicts of interest in this work.

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