



Hereditary Hemorrhagic Telangiectasia - A Rare Cause of Severe Iron Deficiency Anemia

KEYWORDS

epistaxis, malaena, familial, telangiectasias, Osler Weber Rendu Syndrome.

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ABSTRACT *Osler Weber Rendu Syndrome also known as hereditary hemorrhagic telangiectasia (HHT), is a rare autosomal dominant familial disorder manifested by telangiectasias of the skin and mucous membranes. We present a case of young lady with complaints of severe fatigue, malaena and recurrent nose bleeding of unknown etiology and a family history of telangiectasia. The endoscopy revealed multiple vascular ectasias in duodenum, sigmoid colon to caecum. As it is a progressive lifelong disease, we present the history of development of symptoms and complications, results of relevant laboratory tests and endoscopic findings as well as the therapeutic procedures which made the patient dependent on medical outpatient for life.*

BACKGROUND: Osler Weber Rendu Syndrome is an uncommon autosomal dominant disorder characterised by an angiodyplasia in the presence of telangiectasias of the skin and oral mucosa and arteriovenous malformations (AVMs) in the brain, lung, liver and gastrointestinal tract. Its incidence is 1 in 5000-10000 in the general population.¹ Bleeding episodes may occur due to capillary fragility rather than disturbances in coagulation. It is characterised by the classic triad of mucocutaneous telangiectasias with recurrent epistaxis and hemorrhages and inheritance.² The disease has a wide spectrum of presentations varying from asymptomatic to multiple organ involvement. The major cause of morbidity and mortality lies in the presence of multiorgan arteriovenous malformations and the associated hemorrhage.

CASE REPORT: A 20 year old young female born to non-consanguineous parents presented to us with easy fatigability and breathlessness on exertion, palpitations and blackouts of 2yrs duration. She had a history of recurrent spontaneous severe nose bleeding and black coloured stools and history of multiple blood transfusions in the past 2 yrs. There was no history of bleeding gums, abdominal pain, headache, seizures, visual disturbances, hemoptysis, menorrhagia, bluish discoloration of finger tips. She had been treated for epistaxis with electrocauterization therapy many times and admitted to hospital due to exacerbations of anemia and malaena since 2 yrs. Her paternal grandmother and her father also had episodes of epistaxis and gastrointestinal bleeding and died due to severe blood loss suggesting a significant family history. Clinical examination revealed pallor, discoloration and telangiectasias in the oral mucosa and tongue. There were no lesions in the skin and palms. No organomegaly. Cardiovascular and respiratory examination are normal. The laboratory work up revealed Haemoglobin=3.8mg/dl, Total leucocyte count=4000, Platelets=2.5 lakhs, Serum ferritin=3.1, Serum iron=42. Peripheral smear revealed microcytic hypochromic anaemia with normal reticulocyte count. Her coagulation profile was normal, stool occult blood was positive. Serum

for antinuclear antibody, Urine for haemoglobinuria and sickling test were negative. Abdominal ultrasonography, chest radiograph, fundoscopy were unremarkable. Endoscopy of the upper gastrointestinal tract and Colonoscopy revealed multiple vascular ectasias of duodenum, sigmoid colon upto caecum. (Figures-1,2 here).

From these endoscopic, clinical and laboratory findings, the diagnosis of Hereditary Hemorrhagic Telangiectasia was made and the patient has been receiving monthly blood transfusions with preceding steroid treatment. When needed the patient is also given human recombinant erythropoietin and iron therapy, multivitamins, Folic acid and antacids for protection of gastric mucosa on regular follow up.

DISCUSSION: HHT type-1 and type-2 are due to defective Endoglin (ENG) and Activin Like receptor Kinase (ALK1) genes, respectively. Mutations of ENG are located on the long arm of chromosome 9 (9q33-34), whereas ALK1 mutations are on the long arm of chromosome 12 (12q13).^{3,4} HHT type-3 involves mutations of the long arm of chromosome 5 (5q31.1-32) and type-4 maps to the short arm of chromosome 7 (7p14).^{5,6} Patients with the HHT type-1 have higher prevalence of pulmonary and cerebral AVMs, and more severe GI bleeding. Conversely, the prevalence of hepatic AVMs is higher in patients with HHT type-2.⁷ Bleeding tendency in HHT is attributed to localized vessel wall weakness

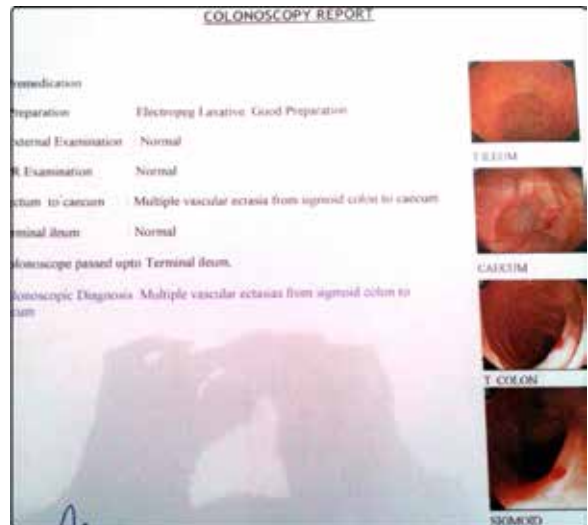
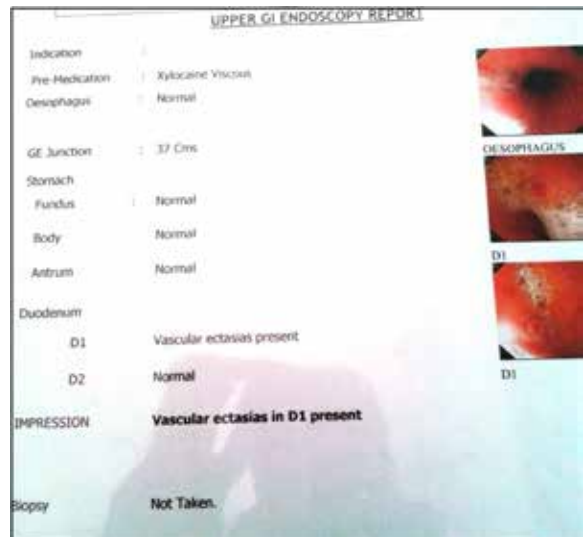
(alteration in the elastic and muscle layers of vessel walls making them more vulnerable to spontaneous rupture and injuries).⁸ Mucocutaneous telangiectasias occur in about 90% of cases of Osler Weber Rendu Syndrome.^{8,9} Nose bleed due to these telangiectasias in the nasal mucosa generally is spontaneous and without severe clinical consequences. However in some cases it may be extremely serious and debilitating. The initial pictures are usually light without hemodynamic or haematological alterations. Telangiectasias of the skin and the

mucosa occur in about 75% of the cases and normally they are considered delayed manifestations. In the patient of the present report telangiectasias appeared after the epistaxis manifested. The visceral involvement occurs in about 25% of the cases with gastrointestinal symptoms predominantly as hematemesis, malaena and hepatomegaly. Its frequency increases with the age, usually manifesting in the fifth or sixth decade of life. Diagnosis is based on the four components of the Curacao criteria, established by the Scientific Advisory Board of the HHT Foundation International i.e;

1) Epistaxis- spontaneous and recurrent; 2) Telangiectasias-multiple, at characteristic sites, including lips, oral cavity, fingers, and nose; 3) Presence of internal lesions- GI telangiectasia, pulmonary, hepatic, cerebral, and spinal AVMs; and (4) Family history: First-degree relative with HHT. The diagnosis is considered definite if any three of the above mentioned criteria are present and possible if any two of the criteria are present.¹⁰ Our case was unique with the presence of all four criteria confirming the diagnosis of HHT. In the absence of pulmonary AVMs, her symptomatology is attributed to anemia resulting from frequent bleeding from her vascular lesions. Pulmonary arteriovenous malformations occur in more than a third of patients with the disease and can cause various complications, such as hypoxia, pulmonary hemorrhage and cerebral embolism.¹² Treatment options for Hereditary Hemorrhagic Telangiectasia should be considered individually for each patient, owing to the diverse clinical manifestations of the disease. Therapy is only palliative and depends on the severity and stage of disease. Some measures including Iron supplements, Blood transfusions and Laser therapy have met with varying degrees of success. Sclerosing techniques have been used to control epistaxis. In patients with recurrent episodes of epistaxis surgery of the nasal septum may be indicated.¹³ The varied treatment modalities include oestrogen, 1-amino caproic acid, cryotherapy, cautery, infrared coagulation, radiofrequency, pulse dye laser, Nd-yag laser and surgical ablation -all of which may be fraught with risks.^{14,15,16,17,18} In the endoscopic therapeutical of the episodes of the gastrointestinal blood loss, photocoagulation or electrocoagulation techniques can be used. Nevertheless this treatment have unsatisfactory results in patients with extensive injuries as those detected in this case.¹⁹ Diffuse lesions also contra-indicate surgical resection of the affected segments. The surgical treatment is more effective when performed for focal angiodysplasias.^{19,20,21} Although case reports and controlled, randomized and double blind studies show the oestrogen therapy's effectiveness, the therapeutic intervention was unsuccessful.^{22,23} So, we continued the medical management.

A study in Italy reported excellent hemostatic results using Nd Yag laser treatment in 8 patients with Osler Weber Rendu Syndrome for the control of epistaxis and oral bleeding.²⁴ This treatment was well accepted by patients and costs were low. However researchers are divided on the efficiency of the use of lasers with Osler Weber Rendu Syndrome patients and there is no specific protocol for their use. The prognosis associated with Osler Weber Rendu Syndrome is good, but the morbidity is significant.²⁵ Moreover, a mortality rate of 1-2% is reported due to complications related to bleeding.²⁶ An early diagnosis is essential in high risk individuals in order to alter their clinical course. It is crucial that a long term follow-up for identification of potential complications is maintained and patients are counselled regarding the autosomal dominant nature of this condition in planning their family.

CONCLUSION: Hereditary Hemorrhagic Telangiectasia is a progressive and extremely debilitating disease. Patients are also exhausted by long lasting treatment, constant monitoring. Also, it is often misdiagnosed and underdiagnosed in the initial presentation. By reporting this case, we wanted to stress upon the importance of careful diagnosis and medical decision making particularly in the approach to such a case of severe anaemia.



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