Hereditary Haemorrhagic Telangiectasia with Severe Anemia and Recurrent CNS Infections

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Abstract
Hereditary Haemorrhagic Telangiectasia, also known as Osler-Rendu-Weber disease is a rare autosomal dominant disorder affecting small vessels of multiple systems whose main pathological change is the presence of abnormal arteriovenous communications. Usually presents as skin and mucosal telangiectasias, epistaxis, gastrointestinal bleeding and visceral arteriovenous malformations. Although the epistaxis and gastrointestinal blood loss can result in anaemia, patients with hereditary haemorrhagic telangiectasia rarely presents as severe anaemia¹ or CNS infections. Herein, we report the case of a 57 year-old man who presented with severe anaemia resulting in congestive cardiac failure with history of recurrent blood transfusions and recurrent CNS infections which ultimately was diagnosed as hereditary haemorrhagic telangiectasia.

Introduction
Hereditary haemorrhagic telangiectasia (HHT) described first in 1865 is an autosomal dominant disorder causing abnormal capillary dilatations or connections called telangiectasia between arterioles and venules. Vascular lesions in HHT may also present as arteriovenous malformations (AVM), or aneurysms especially found in brain, lungs, liver and gastro intestinal system (visceral A-V malformations). Such connections remain usually asymptomatic and can be life threatening ruptured. HHT is usually not considered early in the differential diagnosis of severe anaemia, and careful history with careful examination is required to diagnose the disease.

The clinical profile of HHT, a rare disease with a classic presentation, quite rarely includes severe anaemia and recurrent central nervous system infections. Patients with HHT present normal haemostasis and platelet function, and the recurrent bleeding is therefore related to the telangiectasia. The anaemia can be due to one or both of two factors: recurrent epistaxis and gastrointestinal bleeding and recurrent CNS infections are due to septic emboli from pulmonary arteriovenous malformations.

Case Report
A 57 year old male with history of recurrent blood transfusions was admitted with complaints of dyspnoea on exertion, easy fatiguability and pedal oedema since 1 month. He also had history of recurrent spontaneous epistaxis since childhood around 3-4 episodes per month. Patient gave history of surgical intervention for left parieto-temporal cerebral abcess in 1994 evidenced by giosis on recent imaging. He also had history of recurrent spontaneous epistaxis since childhood around 3-4 episodes per month. Patient gave history of surgical intervention for left parieto-temporal cerebral abcess in 1994 evidenced by giosis on recent imaging. He was diagnosed as having Pott’s spine in 2005 and underwent surgery. At present he is on antituberculous therapy since December 2015 for suspected tuberculoma in cerebral parenchyma.

On probing, patient admitted that some of his family members also had recurrent epistaxis and telangiectasias over fingers and tongue. Neither the patient nor his family members were labelled with any specific diagnosis before this presentation. Detailed family history was taken to document mode of inheritance (Pedigree chart of patient Figure 3).

The family history clearly revealed the epistaxis had occurred in generation in a pattern indicative of autosomal dominant inheritance. Physical examination revealed marked pallor, bilateral pitting type of pedal oedema, raised jugular venous pressure. On careful observation capillary telangiectasias were present on dorsum of tongue and finger tips.

On auscultation, there was a continuous murmur of grade 5/6 heard over the left interscapular region which is suggestive of AV malformation and confirmed by colour doppler imaging.

So in view of recurrent epistaxis, autosomal dominant nature of inheritance from pedigree, Mucocutaneous and visceral telangiectasias diagnosis of HHT was made (Curacao criteria)

Investigations was suggestive of severe anemia which was microcytic and hypochromic with normal thrombocytes and normal coagulation profile. Upper

![Fig. 1: Telengectasias over dorsum of tongue](image1)

![Fig. 2: Telengectasias on fingers](image2)

![Fig. 3: Pedigree chart](image3)

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Hereditary haemorrhagic telangiectasia (HHT) is a rare disorder with prevalence of 1 in 5,000 to 10000 with autosomal dominant transmission, despite the fact that about 20% of the cases may not have a family history. It is thought that the abnormal vessels in HHT develop because of aberrant TGF signaling at some stage during vascular development and mutations of HHT-associated genes. HHT is divided into 4 types on genetic basis. HHT1 is caused by mutations in the gene, ENG (endoglin) on chromosome 9q. HHT2 occurs due to mutations in the gene, ALK-1 (activin receptor-like kinase 1) on chromosome 12q13. The clinical manifestations of HHT are known to be variable and age-dependent. Epistaxis is the first and the most common symptom (90% of patients), 80% of patients have telangiectasia of the skin, lip or mouth. These usually do not cause serious illness; but patients may have a variety of serious complications due to vascular involvement of internal organs, such as the gastrointestinal tract 15%, the lungs 30%, hepatic AVMs < 30%; and the central nervous system 10%, spinal AVMs 1%.

Patients need thorough investigations and close follow up for visceral AV malformations because each may contain clinically silent lesions that can result in sudden morbidity or death. Pulmonary AVM may present with dyspnoea, cyanosis, massive haemoptysis, and haemothorax. For clinical relevance, the diameter of the artery of the PAVM must be ≥ 3 mm. Pulmonary AVMs cause right-to-left shunts resulting in hypoxaemia.

The diagnosis is based on Curacao criterion established in 1999 which include
1. Spontaneous, recurrent epistaxis, nocturnal nosebleeds heighten concern for HHT.
2. Mucocutaneous telangiectases, especially on lips, tongue, oral cavity, fingers and nose.
3. Internal AVM(s) (pulmonary, cerebral, hepatic, gastrointestinal, spinal).
4. First-degree relative with HHT.
Definite diagnosis: 3 or more criteria present
Possible diagnosis: 2 criteria present
Unlikely diagnosis: < 2 criteria present

Our patient had history of recurrent CNS infections which can be due to absence of a filtering capillary bed allowing emboli to reach the systemic circulation.

Cerebral AVMs can lead to headaches, seizures, strokes, transient ischaemic attacks, and both intracerebral and subarachnoid haemorrhage.

Gastrointestinal bleeding (common from stomach and duodenum) can result in iron deficiency anaemia or acute gastrointestinal haemorrhage.

No definitive treatment available. Appropriate management depends on clinical manifestations, site of the disease and remains largely symptomatic. Management options for cutaneous lesions include electrocauterisation with diathermy, sclerotherapy or laser therapy. AV malformations need intervention either as coiling or by clipping; treatment for bleeding is symptomatic and can require iron therapy and blood transfusions. Aspirin and other medicaments that impair haemostasis are contraindicated in such cases.

Bivacizumab is a humanised...
monoclonal anti-VEGF antibody. It inhibits vascular endothelial growth factor A (VEGF-A). VEGF-A stimulates angiogenesis in a variety of diseases including HHT. It significantly reduces epistaxis, causes improvement in GI blood loss and hepatic AV-malformations in latest studies. It is given in dose of 5 mg/kg body wt as intravenous infusion for four weeks. We could not give it to our patient due to cost constraints.

**Conclusion**

Although HHT is a rare disease, it needs to be suspected in a patient with recurrent bleeding, with normal coagulation and can be easily recognised by careful family history and close observation for telangiectasia. Wrong diagnosis delays appropriate therapeutic measures and increases the possibility of chronic complications which can remain unrecognised till advanced stages of the disease.

**References**


