Hereditary Haemorrhagic Telangiectasia - A Rare Cause of Severe Anaemia

Prachee Deshpande*, Shreepad Bhat**, Anup Karmarkar***

Abstract
Hereditary Haemorrhagic Telangiectasia also known as Osler-Rendu-Weber disease is a rare autosomal dominant disorder affecting small vessels of skin and mucosa, usually misdiagnosed because of its non specific symptomatology. This disease usually presents as 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 anaemia. Herein, we report a case of a 60 year-old man with severe anaemia resulting in congestive cardiac failure who ultimately was diagnosed as hereditary haemorrhagic telangiectasia with recurrent epistaxis as a cause of his severe anaemia.

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 if get 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 diagnosis is based on Curacao criterion established in 1999 -2000 which include
1. Recurrent spontaneous nosebleeds (epistaxis)
2. Telangiectasia over skin and mucosa
3. A-V malformations affecting visceral organs
4. Affected first degree relative

Three out of four criterions are required for diagnosis. The clinical profile of HHT, a rare disease with a classic presentation, quite rarely includes severe anaemia. Patients with HHT present normal haemostasis and platelet function, and the recurrent bleeding is therefore being related to the telangiectasia. The anaemia can be due to one or both of two factors: recurrent epistaxis and gastrointestinal bleeding.

Case Report
A 60 year old non-hypertensive male came with complaints of breathlessness on exertion, fatigue and pedal oedema of recent onset. He also had history of recurrent nasal bleed since many years around 2-3 days per week. Recently he had epistaxis almost daily. For this he had consulted many general practitioners and ENT specialists before and was given haematinics, multivitamins, nasal drops without significant improvement in symptoms. On probing, patient admitted that some of his family members also had recurrent epistaxis. 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 1).

The family history clearly revealed the epistaxis had occurred in generation in a pattern indicative of autosomal dominant inheritance. Physical examination revealed marked pallor, weak and sparse hair, koilonychias, pitting bidental oedema, raised jugular venous pressure, congestive hepatomegaly. On careful observation capillary telangiectasia were present on lips, tongue, and nose and finger tips (Figures 2 and 3).

Investigations revealed Hb -2.8 gm/dl, normal total and differential count, severe microcytosis and hypochromia, normal platelet count. MCV -62 fl, Haematocrit-12.3%, Sr iron 15 microgram/dl and Sr TIBC-369 microgram/dl, retic count 1.5%. This suggested severe iron deficiency anaemia. Bleeding and clotting time were normal.

So in view of recurrent epistaxis, autosomal dominant nature of inheritance from pedigree, Muco-cutaneous telangiectasia diagnosis of HHT was made (Curacao criteria)

Patient was further investigated to find visceral AVM and other possible causes for anaemia, especially so as the patient was elderly male. USG showed mild hepatomegaly, X-ray chest – mild cardiomegaly. Stool occult blood was positive. CT PNS was done
to rule out any abnormal AV malformation at nose which showed no abnormal connections. MRI brain was done to rule out intracranial AV malformation, which also was normal. Tc 99m labelled RBC scan was done to look for gastro intestinal tract as a source of bleeding, but that was also negative (Figure 4). Patient also underwent digestive tract endoscopy for mucosal AV malformations. So the stool occult blood was positive due to swallowed blood from epistaxis. Bone marrow biopsy showed marrow with the changes suggestive of severe iron deficiency anaemia. Patient was treated with injectable iron, Vit. B12, Folic acid, diuretics. With this patient’s general condition improved significantly. For epistaxis, local application of oestrogen cream was tried and cauterisation was done. It improved partially.

Conclusion

We had a patient with long standing epistaxis presenting with severe anaemia that turned to have HHT

Discussion

Hereditary haemorrhagic telangiectasia is a rare disorder with prevalence of 1 in 5,000 to10000 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 in to 4 types on genetic basis. It has been proposed that in the case of HHT, disease severity is more pronounced in HHT1 compared to HHT2, with an earlier age of onset for epistaxis, the appearance of telangiectasia, and a higher incidence of pulmonary AVMs. HHT1 is caused by mutations in the gene, ENG (endoglin), encoding endoglin on chromosome 9q. HHT2 occurs due to mutations in the gene, ALK-1 (activin receptor-like kinase 1), encoding activin receptor-like kinase 1 on chromosome 12q13. Results of newer studies indicate two additional genes associated with HHT, MADH4 gene, mutated in a combined syndrome of juvenile polyposis and HHT, and an unidentified HHT3 gene related to chromosome. These events cause alteration in the elastic and muscle layers of vessel walls, making them more vulnerable to spontaneous rupture and injuries. 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 haemoptyysis, 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. Furthermore, the absence of a filtering capillary bed allows emboli to reach the systemic circulation, which may cause recurrent cerebral abscesses and stroke. Transarterial PAVM vaso-occlusion with coils is currently the treatment of choice. 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. In the previously mentioned 9 studies, the most common cause of severe anaemia in patients with HHT was found to be chronic gastrointestinal bleeding (in 70% patients)

Treatment of HHT: No definitive treatment available so far. Appropriate management depends on clinical manifestations, site of the disease and remains largely symptomatic. Management options for cutaneous lesions include electro cauterisation 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.

Recent Advances: Role of Bivacizumab

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.

**Summary**

It is highly unusual for HHT to be accompanied by severe anaemia. Therefore the differential diagnosis in cases of severe anaemia rarely includes HHT.

In summary, 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 postpones appropriate therapeutic measures and increases the possibility of chronic complications which can remain unrecognised till advanced stages of the disease.

**References**