Case Report

# A rare case of pulmonary arterio-venous malformation with recurrent anemia: Hereditary hemorrhagic telangiectasia

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## ABSTRACT

Arteriovenous malformation (AVM) is a rare vascular anomaly of the lung, which manifests predominantly as dyspnea (due to right to left shunting) and paradoxical embolism. Hereditary Hemorrhagic Telangiectasia (HHT) being a rare genetic disorder is one of the most common causes of pulmonary arteriovenous malformation (PAVM). Here we report an interesting case of recurrent anemia in an elderly female, who was subsequently found to have multiple cutaneous and mucosal telangiectasias and a large pulmonary AVM.

**KEY WORDS:** Hereditary hemorrhagic telangiectasia, pulmonary arteriovenous malformation, recurrent epistaxis, telangiectasia

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## INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler-Weber-Rendu disease, is a rare, genetically determined disorder of vascular dysplasia. HHT is an autosomal dominant disorder manifested by mucocutaneous telangiectasias and AV malformations. It occurs in approximately one in 5,000 to 8,000 persons.[1-3] It can manifest at any age and is known to be present in all races, in all parts of the world. The prevalence in India is not known.

Recurrent epistaxis is the most common presentation; however, some patients present with bleeding involving major organs leading to stroke and pulmonary hemorrhage. The disease often remains unrecognized. HHT has varying penetrance and expressivity, often leading to a delay in diagnosis. The onset of symptoms may be delayed until the fourth decade of life. Approximately 90% of the patients manifest by age 40 years or later. In most cases, there is a mutation in one of the two genes that are required for normal angiogenesis.[4,5] Both telangiectasias and AVMs represent a direct connection between arteries and veins, without bridging capillaries. Telangiectasias occur on mucocutaneous surfaces (i.e., nose, gastrointestinal tract, and skin); AVMs develop in larger organ systems (i.e., lungs, liver, and brain).[6] The HHT may also be associated with other diseases, such as, juvenile polyposis syndrome and primary pulmonary hypertension.[7] This disorder is identified by features of telangiectasia, recurrent epistaxis, and a positive family history.[8]

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## CASE REPORT

A 82-year-old post menopausal housewife presented to the Emergency Department with complaints of episodic breathlessness and easy fatigability since five years. Breathlessness was subtle in onset, initially grade 1 New York Heart Association (NYHA) progressing to grade 3 NYHA. There was no history of orthopnea, paroxysmal nocturnal dyspnea (PND), wheezing, chest pain, palpitations, seasonal variations, cough or fever. Since five years, she had been visiting a number of hospitals on Outpatient Department (OPD) basis and was treated symptomatically. She was detected to be anemic five years ago and was transfused with blood. She did not have any other significant past medical illness. She was vegetarian

by diet and was not on anticoagulation. Her obstetric history was uneventful.

On examination, she was afebrile, pale, acyanotic, and normotensive, with a respiratory rate of 28 breaths/minute and a pulse of 108 beats/minute, and did not have signs of heart failure. A cardiovascular and respiratory system examination revealed tachycardia and crepitations in the right infrascapular area. The jugular venous pressure (JVP) was not elevated.

Investigations showed a hemoglobin of 5.3 gm/dl, total leucocyte count of 9100/cumm, with 84% neutrophils, and a platelet count of 1.79L/cumm. The packed cell volume (PCV) was 20.1 and the erythrocyte sedimentation rate (ESR) was 30 mm at the end of one hour and the peripheral smear showed microcytic hypochromic anemia. The chest x-ray (CXR) showed a right paracardiac mass [Figure 1]. Blood gas analysis showed hypoxemia (PO2 of 46.1 mmHg). The sputum Acid-Fast Bacilli (AFB) test was negative. Liver function tests were normal and the coagulation profile was also normal. The iron study showed low ferritin levels. In view of occult blood in stool, an upper gastrointestinal (GI) endoscopy was done, which showed multiple telangiectases in the pyriform fossa, esophagus, and gastric mucosa [Figure 2]. The colonoscopy was unremarkable. However, in view of the right paracardiac mass on chest x-ray, a CT thorax was done, which showed a well-defined serpiginous mass in the right lower zone suggestive of AV Malformation. A pulmonary angiogram was done, which confirmed the presence of large AV malformation in the right lung [Figure 3]. An ultrasound of the abdomen showed mild hepatomegaly. However, there was no intra-abdominal vascular malformation. A nasal endoscopy was unremarkable.

Retrospective enquiry revealed episodic epistaxis in the past and a family history of bleeding tendencies in the form of recurrent epistaxis and gum bleeding (Pedigree chart - Figure 4). Careful examination revealed telangiectasias over the tongue and digits [Figure 5].

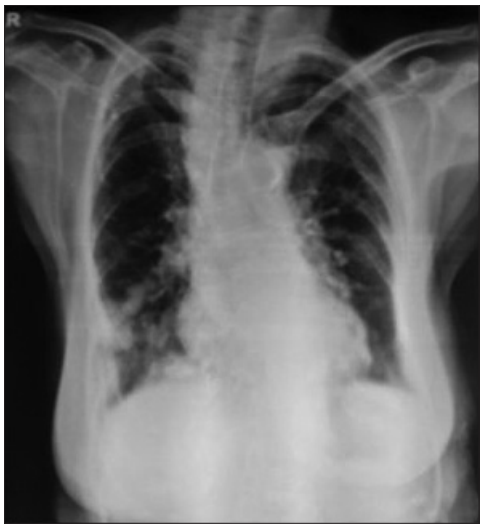

**Figure 1:** CXR showing right lower zone opacity with hilar prominence

The patient was treated with blood transfusion, hemetinics, and oxygen therapy, after which the hemoglobin improved to 10.4 gm/dl. The patient was given the option of coil embolization for pulmonary AVM, but the patient refused the same and is on regular follow-up. In order to screen for cerebral AV malformations, magnetic resonance (MR) angiogram of the brain was done, which was normal.

## DISCUSSION

The syndrome is named after Henri Rendu, Sir William Osler, and Frederick Parks Weber, who published many observations of the syndrome, but it was Sutton (1864), who first described the Osler-Weber-Rendu disease. HHT has four variants that include HHT type-1 to type-4. Type 1 and type 2 are due to defective endoglin- (*ENG)* and activin-like receptor kinase (*ALK1)* genes, respectively.[9,10] The *ENG* and *ALK1* genes are located on the long arms of chromosomes 9 and 12, respectively. HHT type-3 involves mutations in the long arm of chromosome 5 (5q31.1-32) and type-4 maps to the short arm of chromosome 7 (7p14).[11,12] Pulmonary and cerebral AVMs (CAVM's) are more common in patients with type 1 HHT, whereas, severe GI bleed and hepatic AVMs are common in type 2.[13] HHT is inherited as an autosomal dominant pattern. In a case series of seven patients published by Puri *et al.*, in 1996, the median hemoglobin was 4 gm/dl.[14]

Epistaxis occurs due to telangiectasias that develop on the nasal mucosa. These telangiectatic vessels are very fragile and can rupture easily when the nasal mucosa dries up. Epistaxis being the most common symptom in HHT, occurs in 90% of the patients and has a wide range of severity, even among affected family members.[15] The average age of onset of epistaxis is 12 years, with nearly 100% affected by age 40 years.[16,17]

Frequent epistaxis is a common cause of iron deficiency anemia in patients with HHT. The diagnosis of HHT should be suspected when there is a history of recurrent and unprovoked nosebleeds, skin or mucosal telangiectasias, and a family history of epistaxis.

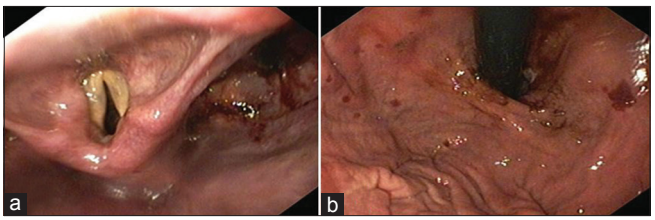


**Figure 2:** Mucosal telangiectasia seen on upper GI endoscopy. (a) Pyriform fossa (b) Stomach

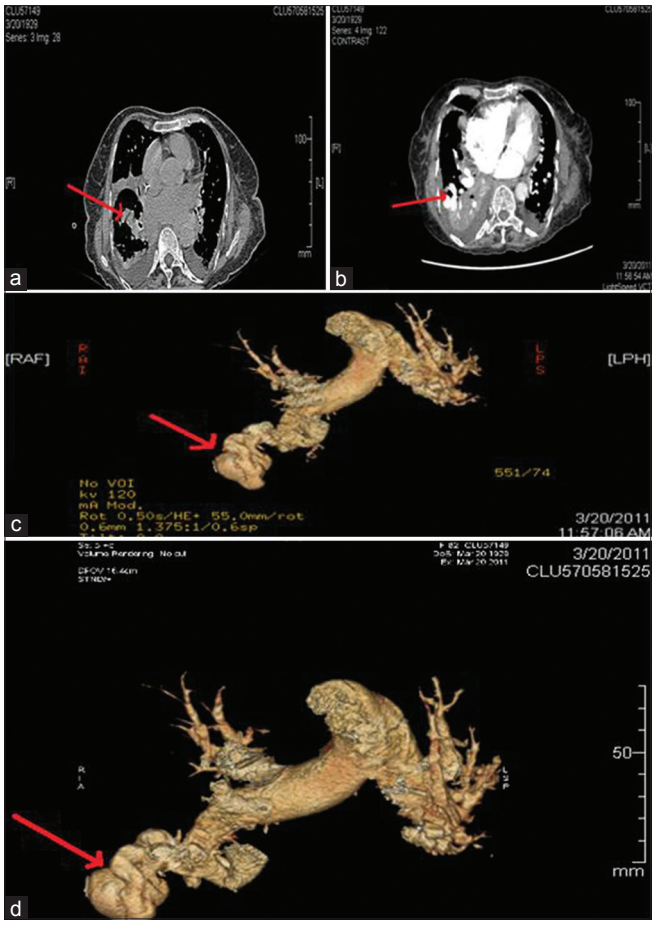


**Figure 3:** (a) Non-contrast CT chest showing a well-circumscribed serpiginous mass in the right lower lobe of the lung (b) Contrast CT chest showing contrast enhancement of the serpiginous mass (c) CT pulmonary angiogram showing large AV malformation arising from the right descending pulmonary artery, drained by an enlarged tributary of the pulmonary vein (d) CT pulmonary angiogram showing large AV malformation arising from the right descending pulmonary artery, drained by an enlarged tributary of the pulmonary vein

Telangiectasias can occur anywhere on the skin, but are most common on the face, chest, and hands. They generally start appearing by age 30 years and increase in number with age. Mucosal telangiectasias can occur anywhere along the GI tract and are often visible on the lips and tongue (as seen in our patient). Apart from epistaxis, the GI bleeding that occurs in approximately one third of the patients is another common cause of iron-deficiency anemia.[18]

About 15 to 30% of the patients with HHT1 develop pulmonary AVMs and about 70% of pulmonary AVMs are due to HHT. Hence, the disorder should be considered in any patient diagnosed with a pulmonary AVM. Similarly, all patients with HHT should be screened for pulmonary AVM.[19,20] The most sensitive test for screening of PAVM is contrast echocardiography. Right-to-left shunt between the pulmonary and systemic circulation across the AVM can lead to hypoxemia. Similarly, paradoxical embolism may lead to cerebrovascular accidents and cerebral abscesses.[21]

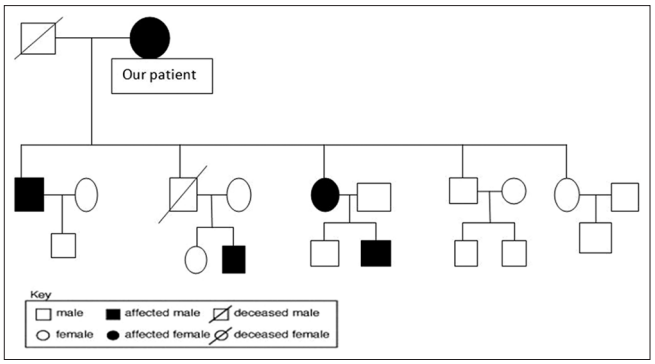


**Figure 4:** Pedigree chart

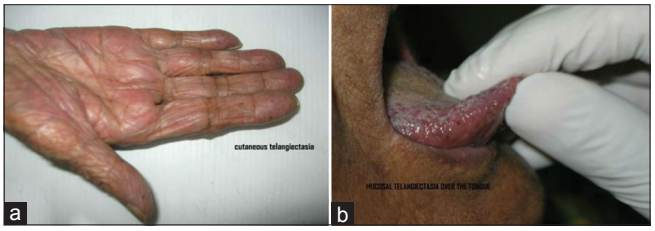


**Figure 5:** (a) Cutaneous telangiectasia over the tips of fingers (b) Mucosal telangiectasia over the tongue

Pregnant women with HHT are at risk of hemorrhage during labor and delivery.[22,23]

Arteriovenous malformation is also seen in the liver (30%) and brain (10%). Hepatic AVMs can lead to portal hypertension, biliary disease, and high output cardiac failure, secondary to shunting between the hepatic artery and vein.[24] Cerebral AVMs can rupture leading to devastating focal deficits and death. MRI is currently the best method to detect these vascular malformations.[25]

Diagnosis and screening done by the 'Curaçao criteria' were developed in 1999 for the diagnosis of HHT.[26] The criteria for diagnosis are based on the four components: (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. (4) Family history: First-degree relative with HHT according to these criteria.

The diagnosis is considered definite if any three of the above-mentioned criteria are present and possibly if any two of the criteria are present.The diagnosis is unlikely if less than two criteria are present. Our patient met all the four components of the criteria confirming the diagnosis. Our patient had spontaneous and recurrent epistaxis along with recurrent gum bleeding, with the background of a family history of epistaxis and gum bleeding. The internal lesions found in our patient were GI telangiectasia and pulmonary AVM. The sensitivity and specificity of these criteria have not been established. It has been said that it may have the risk of missing the diagnosis in children and young adults with undiagnosed PAVM/CAVMs, as these

group of patients develop epistaxis and telangiectasia later in life.

Epistaxis is treated by use of ointments, humidification of indoor air and avoidance of dry climates to decrease drying of the nasal mucosa. Estrogen has been tried (topically or systemically) to help support the nasal mucosa and decrease bleeding. This is based on the belief that nasal mucosa is a hormone-modulated tissue. Laser coagulation of nasal telangiectasias, septal dermoplasty, Youngs procedure, and embolization have been attempted, with temporary benefit.[27,28]

Pulmonary AVMs can be successfully embolized with coils, which require continued surveillance. The current recommendation is to treat any AVM that is at least 3 mm in diameter, although some physicians treat AVMs as small as 1 mm.[29] Other precautions include antibiotic prophylaxis before any invasive procedure, to prevent the risk of infection and cerebral abscess, and use of air filters on all intravenous lines. Scuba diving is not recommended for these patients, because of the risk of decompression sickness. Even though HHT is the most common cause of PAVM, it is worth remembering other causes for the same, which include, trauma, malignancy, hepatopulmonary syndrome, and cardiac surgery.[30] Medical therapies under investigation include vascular endothelial growth factor (VEGF) for the treatment of epistaxis and advanced liver disease and thalidomide for GI bleeding.

## CONCLUSION

Here we report a case of HHT in an 82-year-old woman, who presented with a history of recurrent anemia, epistaxis, and gum bleed in the past, with a background family history of epistaxis and gum bleed in first-degree relatives. On evaluation she was found to have a large pulmonary AVM and GI telangiectasia. Our patient met all the four components of the Curacao criteria, confirming the diagnosis of HHT. Early diagnosis and prompt treatment is required to prevent life-threatening complications. Coil embolization remains the mainstay of therapy for Pulmonary AVM. The HHT Foundation International has helped fund a number of centers of excellence that provide a multidisciplinary approach to the treatment and research of this disease. Patients are encouraged to visit these centers when the need arises and to remain in contact with them about new studies and developing treatments.

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