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Case Report

A neglected cause of anaemia: hereditary hemorrhagic telangiectasia

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ABSTRACT

Hereditary hemorrhagic telangiectasia (HHT) or Osler-Weber-Rendu syndrome is an inherited disorder characterized by vascular dysplasias leading to hemorrhages. If affects approximately 1 in 10,000 Caucasian people. The most common presentation is chronic and recurrent epistaxis whereas bleeding from other sites can lead to life-threatening complications.

Keywords: HHT, Colonic polyp, Iron deficiency anemia

INTRODUCTION

Osler-Weber-Rendu syndrome remains a under diagnosed disease and a diagnosis of exclusion. Mucocutaneous telangiectasia and arteriovenous malformations are the hallmarks of the disease. It is inherited in an autosomal dominant pattern, but the disease presents with many phenotypic variants-varied clinical manifestations, the most common being recurrent epistaxis. Most patients develop symptoms by the age of 40-45 years.[1]

Epistaxis occurs in about 90% of affected individuals.[2,3] Gastrointestinal mucosal telangiectasias lead to hemorrhages in the form of melena, hematemesis and hematochezia.[1] Hepatic vascular dysplasias, though asymptomatic in most cases, can cause portal hypertension and cholestatic jaundice due to pressure over bile ducts.[1]

CASE REPORT

A 70-year-old female presented to the outpatient department with multiple episodes of spontaneous, painless epistaxis and melena, easy fatigability and dyspnea on exertion. Patient previously had painless reddish lesions over the body, predominantly over the palms, soles and tongue for the past 15 years. She gives history of multiple blood transfusions in past. She is known diabetic and hypertensive-adequately controlled at present.

Family history revealed history of recurrent, spontaneous epistaxis in two out of three male offsprings of the second generation and one male member (oldest) of the third generation. Other members of the third generation are not affected as of date. All affected individuals had a similar age of onset of disease (around 4th decade of life) except affected male of third generation who has a significantly early onset of symptoms (2nd decade). Details regarding the patient's parents and her siblings are not known.

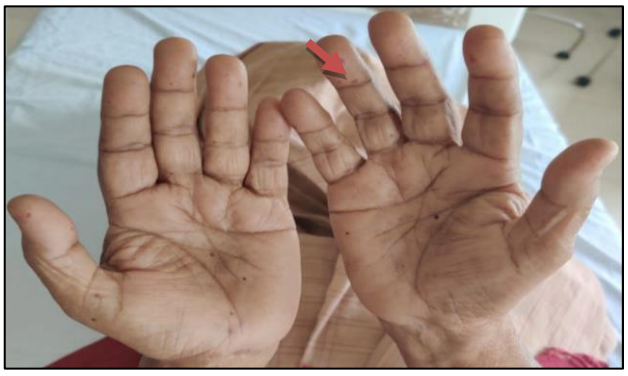

Figure 1: Multiple telangiectasias over both palms.

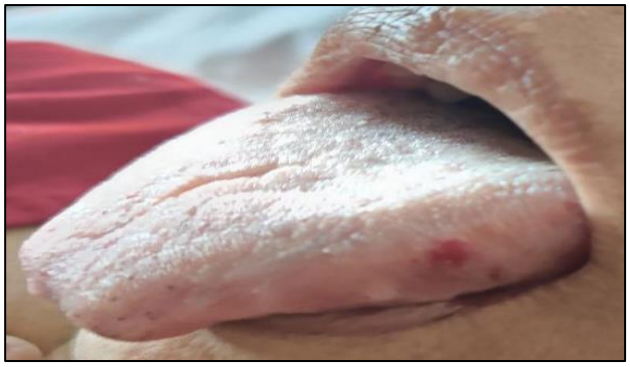

Figure 2: Telangiectasia over the tongue.

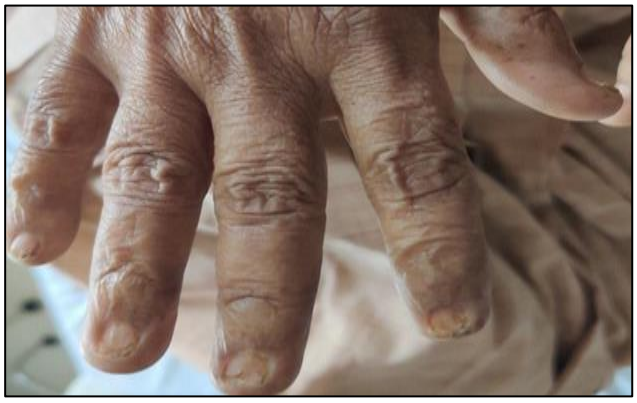

Figure 3: Thin, brittle nails.

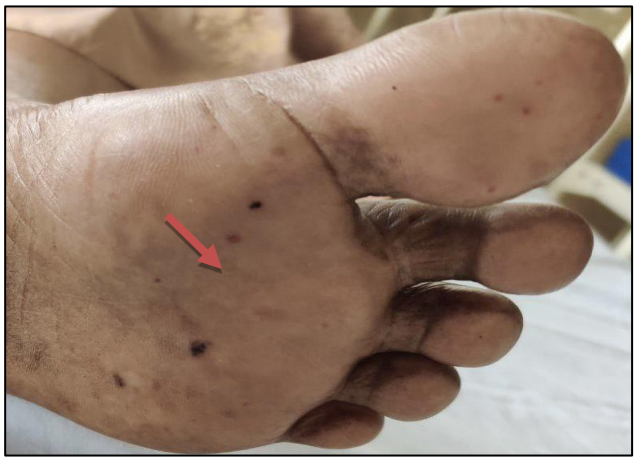

Figure 4: Telangiectasias over the sole.

On examination, she had severe pallor and thin, brittle nails. Telangiectasia was noted in the tongue, skin of both palms and soles. Rest of examination was unremarkable.

Baseline laboratory investigations revealed severe microcytic hypochromic anaemia. Serum iron studies confirmed the cause as iron deficiency anaemia. Stool for occult blood was positive. Renal and liver function tests as well as coagulation profile were found to be within normal limits. Ultrasound of the abdomen revealed hepatic steatosis with mild splenomegaly. Echocardiogram showed evidence of concentric left ventricular hypertrophy with normal ejection fraction. Anti-nuclear antibody test (by immunoblot technique) was done to rule out associated connective tissue disease and was found to be negative.

Patient was initially managed with intravenous tranexemic acid and packed red cell transfusion. Upper GI scopy revealed multiple angioectatic spots in the gastric antrum and duodenum with active ooze-Argon plasma coagulation (APC) was done to achieve hemostasis. After a month, she presented with recurrent malena and colonoscopy was done. A sessile polyp was found in the caecum-polypectomy was done.

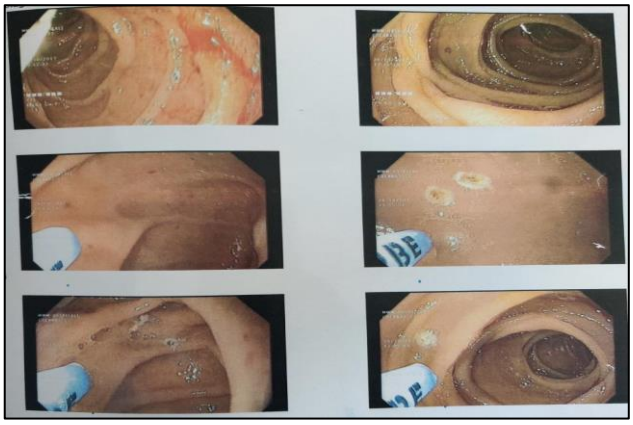

Figure 5: Colonoscopy images of angioectatic spots.

DISCUSSION

HHT is a rare disease contributing to severe anaemia due to haemorrhage from the telangiectasia and AVMs. It needs to be distinguished from Von Willebrand Disease, CREST syndrome and ataxia telangectasia.[1] All these three disorders, apart from having their own characteristic features, do not have AVMs associated with them.

Mutations in various genes can cause HHT, but three genes consistent with the disease are ENG (encodes protein Endoglin), ACVRL1 (encodes protein activin receptor like kinase-1), GDF2 (Growth differentiation factor) and SMAD4 (associated with juvenile polyposis). All the genes involved in the pathogenesis of HHT encode proteins involved in the transforming growth factor-beta (TGF-beta) signaling pathway which plays a major role in the development and maintenance of vascular integrity.[4] Mutations in ENG is associated with HHT-1, whereas mutations in ACVRL1 causes HHT-2.[3] SMAD4 mutations cause juvenile polyposis overlap with HHT (JPHT).[5] HHT-1 is associated with earlier onset of the disease and has vascular malformations in the lungs and brain predominately. HHT-2 has a later onset with vascular malformations in the liver.[4,6] SMAD4 mutations constitute about 1% of the cases.[1]

The pathogenesis of telangiectasis in HHT is due to failure of development of capillaries between the arterioles and

venules.[1] These are attributed to mutations in TGF-beta receptors. When developed, the capillaries have defects in the endothelial cell junctions and perivascular tissues disintegrate which leads to dilatation. Overtime, patients develop arterio-venous malformations (AVMs) causing life-threatening haemorrhages. Common sites of AVMs include the lungs, brain and spinal cord, conjunctiva, retina and liver. Rarely, they can occur in the kidneys and pancreas. Large AVMs can cause significant left-to-right shunting of blood, leading to high-output cardiac failure.[7]

The inheritance pattern of HHT is autosomal dominant and all members of an affected family tend to have the same mutation. One copy of the mutant gene is enough to cause disease in the offspring (50% chance) with male and female offspring's being affected equally.[1,8]

Diagnosis of HHT is based on Curaçao's diagnostic criteria established in 1999 June which includes 4 domains- epistaxsis, telangiectasia, visceral telangiectasia and a positive family history.[3] Presence of 3 out of the 4 domains confirms the diagnosis. Genetic testing plays an important role for asymptomatic children of an affected parent.[8] Blood work up to look for iron deficiency anemia and a coagulation profile to rule out bleeding disorders are done as preliminary investigations. Screening for AVMs is recommended by modalities such as MRI brain with gadolinium (brain AVMs), Contrast echocardiogram and CECT thorax (pulmonary AVMs) and ultrasound/CT/MRI abdomen (hepatic AVMs).

Histopathologically, there is marked irregular dilatation of capillaries lined by flat endothelial cell.

Treatment of HHT is based on the presenting symptom of the patient. For epistaxis, nasal lubrication, oral Tranexemic acid, sclerotherapy or surgical ablation is considered. Patients with pulmonary AVMs required antibiotic prophylaxis for minor procedures and close follow-up of the AVMs. Transcatheter embolization therapy with coils or plugs is recommended when the size is large. Brain AVMs are treated surgically or by embolization techniques whereas liver AVMs are treated only when associated with symptomatic liver failure or high output cardiac failure. In refractory cases, liver transplantation is the treatment of choice. In case of bleeding gastrointestinal AVMs, endoscopic cautery is done. Iron deficiency anaemia can be severe and is treated by iron replacement and blood transfusions. Refractory bleeding is treated with intravenous/oral tranexemic acid. Estrogen-progesterone based therapies have been used to treat the disease as they increase nasal squamous epithelium but they are associated with side-effects like gynecomastia, weight gain, loss of libido in men, coronary events and venous thromboembolism.[7] Anti-angiogenic agents like intravenous Bevacizumab, a recombinant humanized monoclonal antibody that inhibits VEGF are under investigation.[1,7]

Our patient has colonic polyp associated with HHT which contributes to about 1% of all cases of HHT. The third generation of the patient's family seems to have an earlier onset of symptoms. Since the other members of her family have less severe symptoms, they have not been evaluated yet.

CONCLUSION

HHT is a disease-causing severe anaemia and interfering with the patient's quality of life. At present, treatment is aimed at amelioration of the presenting complaint. Several drugs including anti-angiogenic agents are under investigation for the treatment of HHT and related disorders and show promising results.

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