Hypergonadotropic Hypogonadism as a Rare Association with Hereditary Hemorrhagic Telangiectasia

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ABSTRACT

Hereditary Hemorrhagic Telangiectasia (HHT) also known as Osler Weber Rendu syndrome is a rare autosomal dominant genetic disorder that causes aberrant vasculogenesis in the skin, mucus membranes and major organs such as lungs, gastrointestinal tract, liver and brain. A 48 years old gentleman presented to our tertiary care hospital with complaints of recurrent episodes of epistaxis for the past 30 years. Epistaxis occurs on and off for the past 30 years at varying frequencies between 1 - 2 episodes per week, approximately 10 - 15 drops from both nostrils, occurring predominantly on straining, resolving spontaneously. There was no history of trauma and bleeding episodes were not associated with nose picking. Patient presented to us with history of one episode of melena and haematemesis associated with easy fatigability.

KEYWORDS
Telangiectasia, Vasculogenesis, Hereditary hemorrhagic, Arteriovenous

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INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT) also known as Osler Weber Rendu Syndrome is a rare autosomal dominant genetic disorder that causes aberrant vasculogenesis in the skin, mucus membranes and major organs such as lungs, gastrointestinal tract, liver and brain.[1] Patients present with recurrent epistaxis, acute and chronic gastrointestinal bleeding, iron deficiency anemia and rarely fatal hemorrhagic manifestations of Arteriovenous Malformations (AVMs) in several organ systems.[2] It is therefore critical to have a thorough understanding of this disease and its various manifestations, both known and unknown to get diagnostic screening and prevent its complications. Hypergonadotropic Hypogonadism also known as primary hypogonadism is the most common cause of abnormal sexual differentiation and has an incidence of 1 : 500 - 1000 population.[3] To our knowledge, the case described here is the first HHT case with a presentation of infertility secondary to primary hypogonadism in addition to the classical symptoms.[4-7]

CASE PRESENTATION

A 48 years old gentleman presented to our tertiary care hospital with complaints of recurrent episodes of epistaxis for the past 30 years. Epistaxis occurs on and off for the past 30 years at varying frequencies between 1 - 2 episodes per week, approximately 10 - 15 drops from both nostrils, occurring predominantly on straining, resolving spontaneously. There was no history of trauma and bleeding episodes were not associated with nose picking. Patient presented to us with history of one episode of melena and haematemesis associated with easy fatigability. There was no history of abdominal distention, jaundice, nor was there any history to suggestive cardiac involvement. There was no history suggestive of connective tissue disorder or vasculitis such as photosensitivity, fever, weight loss, joint pains, haematuria or rashes over the body. Patient is married since 25 years and is reported to suffer from infertility since marriage, however gives no history of loss of libido, difficulty in attaining erection and performing sexual intercourse. Both his father and brother give similar history of recurrent epistaxis. There was no other notable medical history. On examination, it was noted that our patient was severely anaemic, tachycardia, hypotensive with bilateral pitting pedal oedema. There were multiple telangiectasias in the oral cavity, lips, eyes, and front and back of chest (Figure 1). Examination revealed gynecomastia, absence of secondary sexual characteristics, bilateral absent testis.

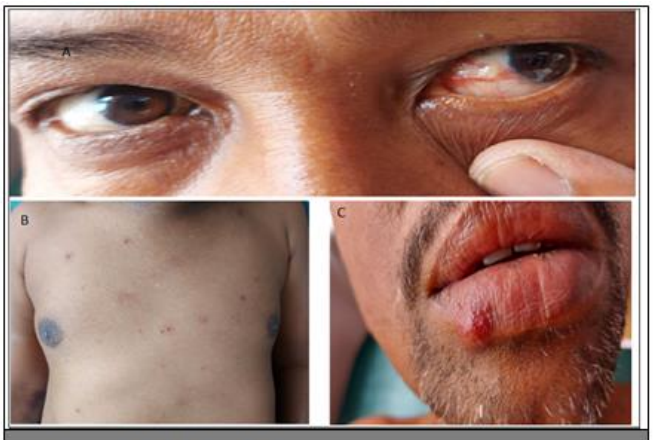

Figure 1 (A,B,C). Telangiectasias in Eye and Telangiectasias Over Chest Wall and Lips.

Routine hematological tests were remarkable for anaemia (Hb - 5.1 g %), severe iron deficiency (Serum iron – 12 ug / dl, ferritin – 3.0 ng / dl). Endocrine panel showed elevated luteinizing hormone of 17.20 miu / ml (1.24 - 8.62 miu / ml), follicle stimulating hormone of 43.06 miu / ml (1.42-15.40 miu / ml) and reduced total testosterone levels of 135.46 mg / dl (168 - 750 ng / dl). Karyotyping ruled out chromosomal abnormalities. ANA and ANCA profile were negative. Renal function, liver function tests and coagulation profile were unremarkable. Viral serology panel was negative for HIV, *Hepatitis B* and *Hepatitis C*. Ultrasound of abdomen and pelvis with hepatic Doppler parameters showed hepatic AVMs, ultrasound scrotum confirmed the absence of testis bilaterally in the scrotal sac, pelvic and abdominal cavity. Upper GI endoscopy showed presence of multiple gastric and duodenal telangiectasias (Figure 2).

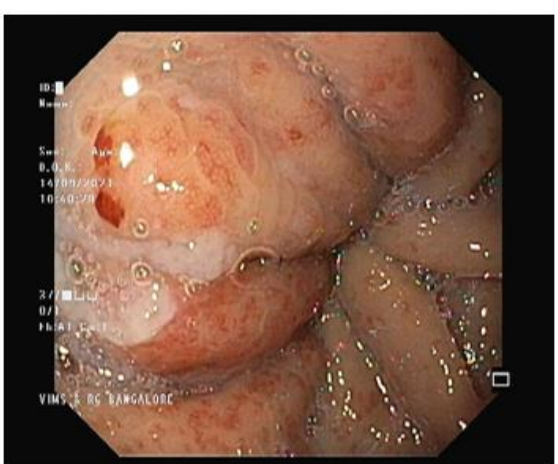

Figure 2. Gastric Telangiectasia.

CT pulmonary angiography confirmed the presence of pulmonary AVMs (Figure 3). Overall history, imaging findings were suggestive of HHT spectrum disorder.

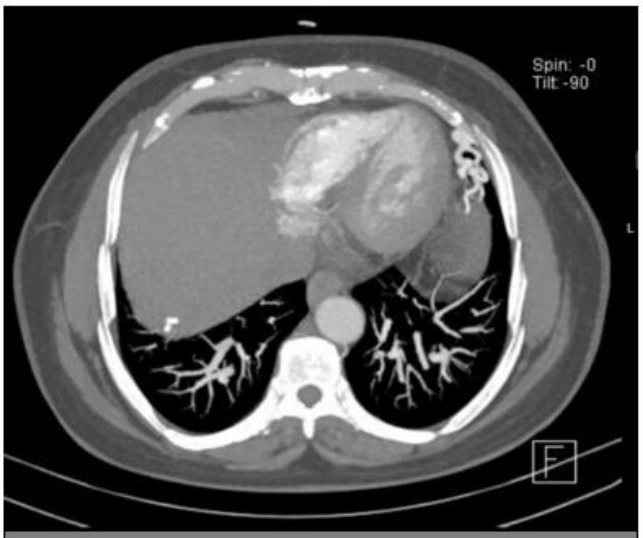

Figure 3. Pulmonary AVMs.

Clinical diagnosis: Based on the international consensus criteria *i.e.,* Curacao criteria, patient was labelled as definite HHT as all 4 criteria were met and further genetic testing was not performed. Patient's epistaxis was conservatively managed, blood was replaced, iron deficiency was appropriately corrected and antifibrinolytics were administered. Patient improved with these measures. Testosterone replacement was done and patient was advised regular follow up.

DISCUSSION

HHT is a rare autosomal dominant genetic disorder resulting in the formation of anomalous vasculature. Clinical features include childhood onset recurrent epistaxis, gastrointestinal bleeding, iron deficiency anemia, mucocutaneous telangiectasias, AVMs most commonly in the hepatic vasculature followed by the pulmonary and cerebral vasculature in descending order.

The four main genes implicated are ENG (Endoglin), ACVRL1 (Activing Receptor - Like Kinase) SMAD (Mothers Against Decapentaplegic Homolog) and GDF2 (Growth Differentiation Factor). Mutations in these genes disrupt the transformation growth factor beta (TGF-ß) signaling pathway leading to the constellation of features found in this disorder.

The patient described here matched all four clinical criteria defined by the Curaçao criteria *i.e.*

- Recurrent spontaneous epistaxis.
- Positive family history of HHT.
- Mucocutaneous telangiectasia.
- Any one visceral lesion with AVMs, excluding the need for genetic testing.

Based on the history of infertility, elevated gonadotropin releasing hormones, reduced testosterone and absence of testis, primary hypogonadism most likely due to testicular dysgenesis was thought of Klinefelter's syndrome, the most common cause of adult hypogonadism was excluded by karyotype analysis. ENG, ACVRL1, SMAD4 all belong to the TGF - ß superfamily. Certain HHT variants are also associated with mutations in Bone Morphogenetic Protein (BMP). This TGF - ß superfamily uses ligand specific pathways between SMAD, activing receptor - like kinase, BMPs playing an important role in the formation of both ovaries and testes in the developmental window. This process has been implicated in the onset of testicular dysgenesis. Both HHT and testicular dysgenesis are rare and the concurrence of these events led us to believe a possible association and must be included in the symptom cluster. Management focuses solely on the presentation. In case of epistaxis, local pressure along with nasal packing and cauterization may be effective for anterior bleeds. Posterior bleeds may require surgical intervention. Multiple anti estrogen trials have showed Tamoxifen 20 mg / day are also associated with good outcomes. Bevacizumab, an inhibitor of Vascular Endothelial Growth Factor (VEGF) used intravenously or by nasal spray has been used in refractory cases both for epistaxis and for organ involvement. For gastrointestinal bleeds, endoscopic ablation therapy is essential, for pulmonary AV malformations embolotherapy may be required and can be so severe as to necessitate lung transplantation. Along with this specific management, blood transfusion and iron infusions must be given appropriately.

CONCLUSION

HHT has a large spectrum of clinical manifestations and can be potentially fatal due to massive internal haemorrhage. To our knowledge, this is the first case of HHT presenting with hypergonadotropic hypogonadism likely due to testicular dysgenesis as a result of HHT spectrum genetic mutations. Early diagnosis and treatment can help in administering prompt treatment and improve the patient's quality of life.

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