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CASE PRESENTATION AND REVIEW OF LITRATURE FOR A RARE CASE OF HEREDITORY HEMORRHAGIC TELANGIECTASIA AS SECONDARY POLYCYTHEMIA

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ABSTRACT

Hereditary hemorrhagic telangiectasia (also known as Osler-Weber-Rendu disease) is an autosomal dominant disorder that results from multisystem vascular dysplasia. It is characterized by telangiectasias and arteriovenous malformations of skin, mucosa, and viscera. Epistaxis is the most common presenting problem, occurring in 90 percent of affected patients. Diagnosis is clinical and made using the Curacao criteria. Patients usually seek medical attention due to bleeding manifestations from telangiectasias or arteriovenous malformation. Herein we report a case who presented to us mainly due to features of hyperviscosity of blood due to secondary polycythemia which developed due to an underlying Pulmonary arteriovenous malformation.

KEYWORDS: HHT, Osler-Weber-Rendu disease, Pulmonary arteriovenous malformation.

INTRODUCTION

Hereditary Hemorrhagic Telangiectasia (HHT; also known as Osler-Weber-Rendu Disease) is a relatively common disorder inherited in an autosomal dominant fashion that results from

multisystem vascular dysplasia and is characterized by telangiectasias and arteriovenous malformations (AVM) of skin, mucosa and viscera. All ethnic and racial groups are affected by HHT and it is seen over a wide geographic distribution with an overall frequency of 1 per 5000 to 10 000 persons. The diagnosis of this disorder is made on the basis of the Curacao criteria established in June, 1999. The diagnosis is confirmed by the presence of at least three of four manifestations.[1] Epistaxis is the most common presenting problem, occurring in 90 percent of affected patients. Approximately 15 to 30 percent of patients with HHT will have an AVM in the lungs and more than 10 percent will have one in the brain. The symptoms of HHT are often unrecognized. Many patients, even those with affected family members, may go undiagnosed. Pulmonary arteriovenous malformations (PAVM) have been shown to be associated with disabling and life-threatening complications, such as stroke, TIA, cerebral abscess, massive hemoptysis and spontaneous hemothorax. Our patient presented with features of hyperviscosity due to polycythemia which developed secondary to a complex Pulmonary arteriovenous malformation (PAVM).

CASE REPORT

A 23 year old boy an engineer born by a non-consanguineous marriage, presented to us with complaints of dizziness/light headedness from past 2-3 months and one episode of loss of consciousness for around 1 minute 3 days before presenting to us. There was no history of fever, headache, vomiting, diplopia, tinnitus, hearing disturbances, palpitations or exertional dypnoea. He gave past history of recurrent and spontaneous epistaxis which started around the age of 8 years but no history of bleeding from any other site. On probing patient admitted that few of his family members also had episodes of recurrent and spontaneous nasal bleeds. A detailed family history was taken and a family tree (Figure 1) was prepared which clearly indicated that epistaxis occurred in generations in a pattern suggestive of autosomal dominant inheritance. His grandmother had 3 episodes of hemorrhagic stroke between 65 to 70 years of age and finally succumbed to it. On examination vitals were stable, grade 3 clubbing and central cyanosis (Figure 2) was seen, heart sounds were normal and no added murmur heard. On auscultation of chest a bruit was heard in right infrascapular region best heard with patient upright and in deep inspiration. No organomegaly was found and fundus was within normal limit. Routine investigations (Table 2), revealed presence of polycythemia, hypoxemia, and decreased iron stores. ECG revealed left ventricular hypertrophy, Xray chest (Figure 3) revealed an ill-defined peripheral radio-opacity in lower lobe of right lung with radio-opaque cords arising from lesion and extending into ipsilateral hilum. Hemoglobin electrophoresis

was normal, a nasal endoscopy was performed to look for cause of epistaxis and it revealed multiple telangiectasias (Figure 4). 2D-ECHO was normal. Based on history, physical examination and investigations done so far a possibility of Pulmonary AVM was kept and therefore a contrast 2D-ECHO using agitated saline was done, in which micro bubbles appeared in left atrium approximately 3 cardiac cycles after they were seen in right atrium (Figure 5), suggestive of an Intrapulmonary Shunting. This finding was confirmed using a CT Pulmonary Angiography which revealed a Complex High Flow A-V Malformation (Fistula) in lower lobe of right lung (Figure 6). In view of presence of spontaneous recurrent epistaxis, nasal mucosa telangiectasias, visceral involvement (Pulmonary AVM) and presence of epistaxis in other family members with an autosomal dominant mode of inheritance from pedigree, a final diagnosis of Hereditary Hemorrhagic Telangiectasia (Curacao Criteria) with polycythemia secondry to pulmonary A-V Fistula was made. Patient was further investigated to look for AVM elsewhere. MRI brain, MR Angiography of cerebral and spinal vessels and, hepatic Doppler were all normal.

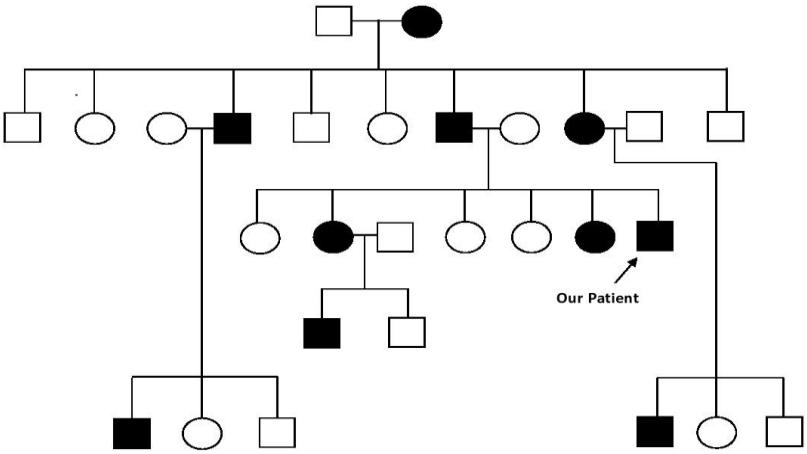


Figure 1: Pedigree chart of patient – Autosomal Dominant Inheritance.

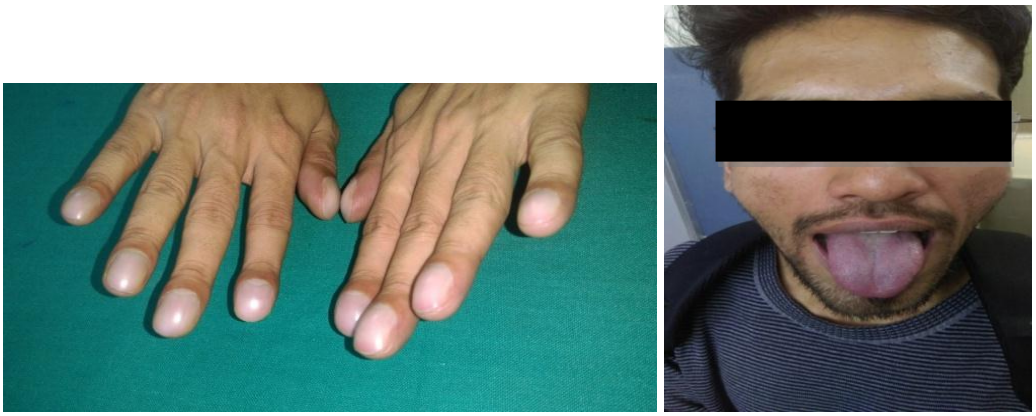


Figure 2: Clubbing and Central cyanosis in Patient.

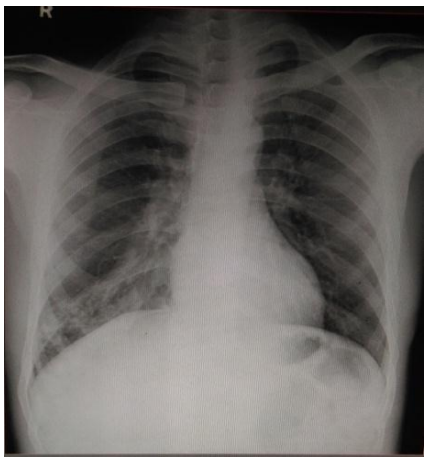


Figure 3: Xray Chest.

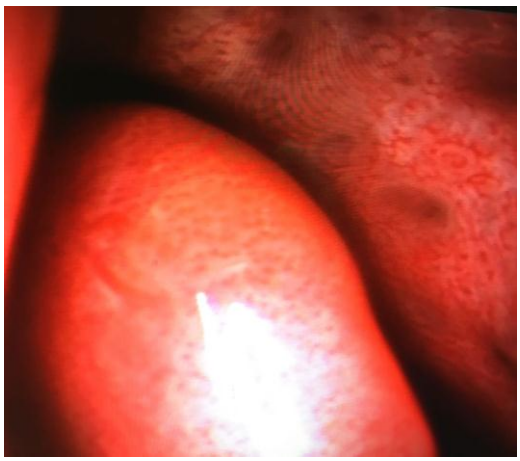
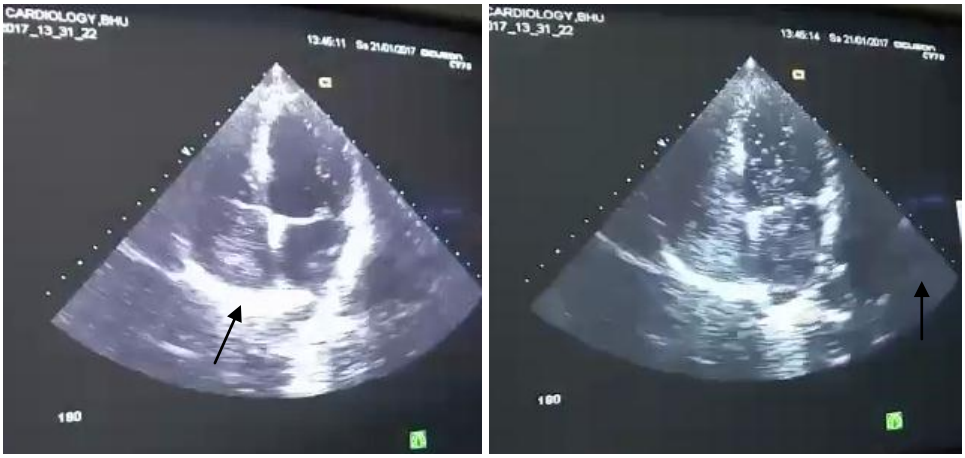


Figure 4: Nasal Telangiectasias.



A **B**

Figure 5: (A) Contrast seen in left atrium as shown by arrow (B) Contrast.

Appeared in right atrium after 3 cardiac cycles

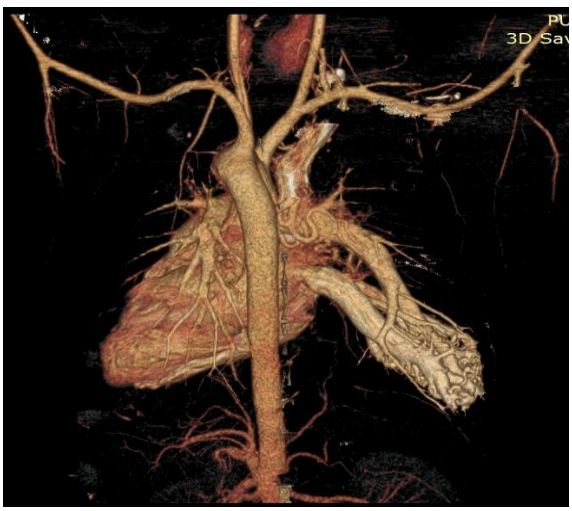


Figure 6: 3D reconstruction image of Pulmonary CT Angiography showing A complex AVM.

Table 1: Diagnostic Criteria for HHT (Curacao Criteria).

Criteria	Characteristics
Epistaxis	Spontaneous, recurrent nosebleeds
Family history	A first-degree relative with HHT
Telangiectasias	Multiple telangiectasias at characteristic sites (eg. Lips,oral cavity, fingers, nose)
Visceral lesions	Examples include gastrointestinal telangiectasias (with or without bleeding), pulmonary AVM, hepatic AVM, cerebral AVM, spinal AVM

Table 2: Routine Investigations.

Investigation	Values	Normal Range	Unit
Hemoglobin	**21.7**	11-16	mg/dl
TLC	4430	4-10 x 10^3	per µl
DLC	$N_{48}L_{39}M_{5.7}E_{6.5}$		
Platelets	168000	1.5-4.5 x 10^6	per µl
Hematocrit	67.2		%
PO2	**49.4**	80-100	mm of Hg
SO2	**83.4**	95-100	%
LDH	447	230-460	U/L
SGOT/SGPT	20/23	10-40	U/L
Alkaline Phosphatase	127	30-120	U/L
Total bilirubin	**2.7**	0.1-1.2	mg/dl
Direct bilirubin	0.1	0.01-0.3	mg/dl
Total Protein	7.6	6.4-8.5	gm/dl
Albumin	4.7	3.2-5.5	gm/dl
Creatinine	0.8	0.5-1.5	mg/dl
Urea	18	15-45	mg/dl
Sodium	141	135-145	mmol/L
Potassium	3.9	3.5-5.5	mmol/L
Iron	189	58-158	µgm/dl
TIBC	315	250-425	µgm/dl
Ferritin	**18.1**	20-300	ng/ml

DISCUSSION

Hereditary Hemorrhagic Telangiectasia also known as Osler-Weber-Rendu Syndrome was first described in the nineteenth century as a familial disorder causing bleeding from nose and gastrointestinal tract and abnormal vascular structures. In 1909, Hanes coined the term Hereditary Hemorrhagic Telangiectasia, in acknowledgement of the three features, which by then defined the disorder. Currently, five types of Hereditary Hemorrhagic Telangiectasia (HHT) are recognized.[2] The majority of HHT patients will have HHT1 due to mutations in ENG encoding endoglin or HHT2 due to mutations in ACVRL1 encoding activin receptor-like kinase (ALK1). One to two percent of cases have mutations in SMAD4, mutations that

also cause the gastrointestinal epithelial precancerous state of juvenile polyposis. The mainstay of diagnosis remain the Curaçao Criteria, international consensus diagnostic criteria developed between 1997 and 1999 and recently validated.[1] An individual has a diagnosis of "definite HHT" if three criteria are present; "suspected HHT" if two are present, and "unlikely HHT" if only one is present. For patients with definite clinical HHT, molecular testing is not required to confirm their diagnosis. Genetic testing is most helpful in the setting of a potentially unaffected family member in whom the diagnosis of HHT cannot be excluded clinically.

Recurrent spontaneous epistaxis is the most common symptom of HHT and often leads to iron-deficiency anemia.[3] Epistaxis appears before the age of 20 years in about 50% of patients, with 78 – 96% of all HHT patients developing it eventually, 80% of patients have telangiectasia of lip or mouth. Approximately 23% of HHT patients will harbour a Cerebral Vascular Malformation (CVM).[4] The rationale for screening for CVMs in HHT, is that screening will detect a treatable CVM prior to the development of a life-threatening or debilitating complication like stroke. Although 80% of patients with HHT have gastric or small intestinal telangiectasia on endoscopy or capsule examination, only 25-30% of patients will develop symptomatic GI bleeding which usually does not present until the fifth or sixth decades of life. Liver Vascular Malformation are present in 32-78% of HHT patients. The clinical presentations of liver VMs include high-output heart failure, portal hypertension and biliary necrosis. Approximately 70% of the cases of PAVM are associated with HHT. Conversely, approximately 15 to 35% of patients with HHT have PAVM.[4] Fifty-three to seventy percent of PAVM are found in the lower lobes. PAVM can be classified as either simple or complex. Eighty to ninety percent of PAVM are of the simple type defined as those with a single feeding segmental artery and a single draining vein. The rest are complex, with two or more feeding arteries or draining veins. Symptoms in early life may vary from being totally absent to severe with cyanosis, congestive heart failure, and even fulminant respiratory failure. The most common complaint in symptomatic patients with PAVM is epistaxis, which is caused by bleeding from mucosal telangiectasias and reflects the high incidence of HHT in patients with PAVM. Dyspnea is the second most common complaint in patients with PAVM, and the most common complaint referable to the lungs in such patients. Some patients also have platypnea. Hemoptysis is the third most common symptom. Many patients with HHT have iron deficiency anemia caused by frequent epistaxis and GI bleeding. Treatment options include iron supplementation either orally or by intra-venous infusion.

Blood transfusions may be required for some patients. Management of chronic recurrent epistaxis in HHT includes measures to maintain integrity of the nasal mucosa, such as humidification. Procedural therapies for chronic HHT related epistaxis include endonasal laser, electrical or chemical coagulation techniques, replacement of the fragile endonasal mucosa by skin or buccal mucosa (dermoplasty), nasal artery embolization and closure of the nasal cavity. For CVM effective treatment strategies include embolization, microsurgery and stereotactic radiation, or combinations of these. Primary objectives of treatment of PAVM, include prevention of CNS complications especially brain abscesses, and relief of hypoxemia when present. Treatment of PAVM by transcatheter occlusion using detachable steel coils (embolization therapy) decreases right-to-left shunting, thus improving arterial blood gases and dyspnea. Treatment of PAVMs with feeding vessels of 3 mm diameter or more is justified, even if PAVMs are asymptomatic; smaller PAVMs may also be occluded when technically feasible and right-to-left shunting is present.[5,6] Conversely, embolization of PAVMs with large feeding vessels (up to 14 mm) may be difficult and require specific devices such as balloons or Amplatzer occluders.[7] Patients who have AVMs, as well as those who have not yet been screened, should receive antibiotic prophylaxis for any procedures that have a risk of bacteremia (e.g., dental) to avoid the possible development of brain infection and abscess formation. Patients should have air filters on all intravenous lines, and it is recommended that they not scuba dive because of the risk of decompression sickness.[8] Management of GI bleeding in HHT involves treatment of the iron-deficiency/anemia and therapies to reduce GI bleeding. Current treatment options to reduce chronic GI bleeding in HHT include hormonal therapy (estrogen-progesterone preparations or danacrine), anti-fibrinolytics (aminocaproic acid or tranexamic acid),and local endoscopic therapy, using argon plasma coagulation (APC) or ND-YAG laser, may be beneficial in reduction of HHT-related GI bleeding[3] Hepatic disease leading to liver failure requires liver transplantation. Heart failure can be treated medically but may require heart transplantation. Our patient was managed with phlebotomy with target of relieving hyperviscosity symptoms and to maintain a hematocrit below 65%. After phlebotomy patient was completely relieved of symptoms with which he presented to us. Iron supplementation was also started to avoid iron depletion. For embolotherapy he was referred to other center as it is not being done at our center.

CONCLUSION

We describe the case of a 23 year old Indian male patient who presented to us with symptoms of hyperviscosity of blood due to polycythemia secondary to a complex PAVM who was eventually diagnosed to have HHT. Any patient with a PAVM should be evaluated to rule out HHT as 70% of PAVM are associated with it.

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