CASE HISTORY

HEREDITARY HEMORRHAGIC TELANGIECTASIA (OSLER-WEBER-RENDU SYNDROME)

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A 65-year-old male born to no consanguineous parents presented with multiple red raised lesions on the tongue and both hands of almost 25 years duration. He also had breathlessness on exertion and easy fatigability since 15 years. He had a history of multiple blood transfusions in the past two decades, and multiple episodes of epistaxis, palpitations, and frequent blackouts. He had history of intracerebral bleed 30yrs back [Figure 1].

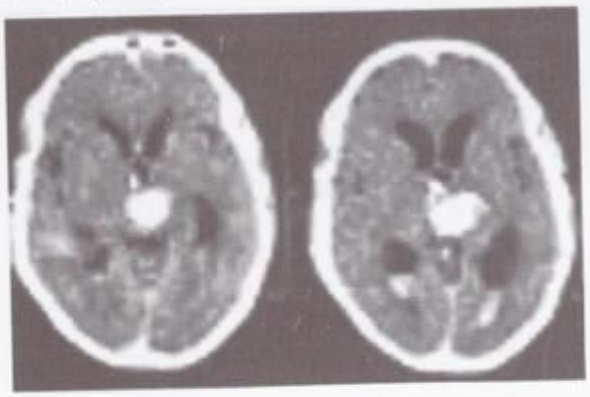

Figure 1; CT Brain with bleed due to AV malformation

There was no history of bleeding gums, haemétemesis, abdominal pain, melana, headaches, seizures, visual disturbances, hemoptysis, or bluish discoloration of fingertips or nose. There was history of similar lesions being present in 10 of his immediate family members [Figure 2]. Her two elder sisters died of severe bleeding from such lesions in the mouth and hands; also, her father suffered from hemiplegia.

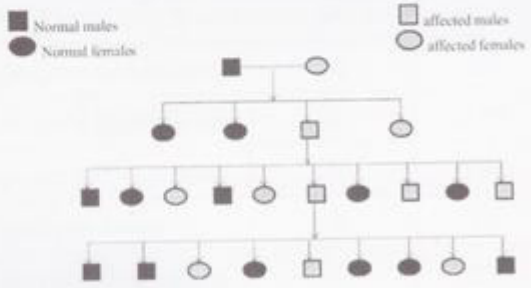

Figure 2: Family Tree of our patient with OWR Syndrome(HHT)

Clinical examination revealed pallor and absence of organomegaly. Dermatologically, multiple erythematous macular blanch able lesions on both palms; multiple erythematous compressible nonpulsatile papulonodular lesions on the tongue, and multiple petechiae over the palate [Figure 3] were evident.

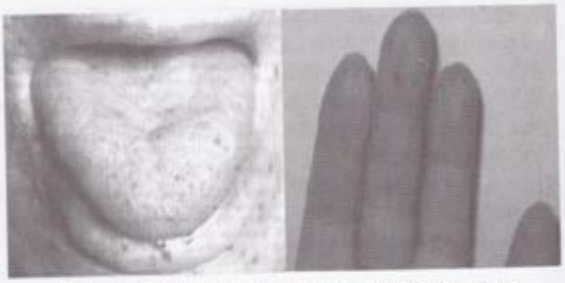

Figure 3; Mucocutaneous Talangiectasias

Investigations revealed microcytic hypochromic anemia, normal reticulocyte count, and normal coagulation profile. Serum for antinuclear antibody (ANA), urine for hemoglobinuria, and Sickling test were negative. Abdominal ultra sonogram, chest radiograph, and fundoscopy were unremarkable. Upper GI endoscopy [figure 4] revealed multiple raised red lesions in the gut wall right from oropharynx down to jujenum. Neither colonoscopy nor abdominal, pulmonary, and renal angiograms revealed any AVMs in other organ systems.

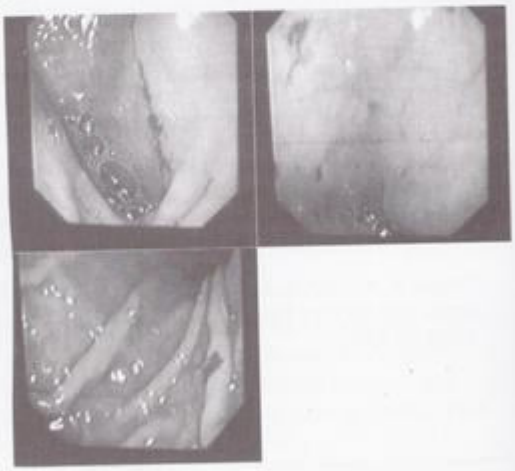

Figure 4a: Talangiectasias in stomach and duodenum endoscopic view

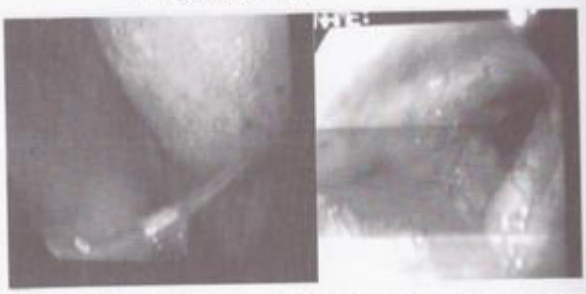

Figure 4b: Talangiectasias on tongue, buccal mucosa and larynx endoscopic view

Patient reassured explained about the diagnosis was treated for anemia of blood lose. Given iv supplemental iron infusion and advised follow up.

Literature Review

Introduction - Heridetary heamorrhagic talengectasia (HHT, Osler-Weber-Rendue syndrome), an autosomal dominant vascular disorder, had a variety of clinical manifestations. Among the most common are epistaxis, gastrointestinal bleeding, and iron deficiency aneamia, along with charectaristic mucocutaneous talengectasia. In addition AV malformation (angiodysplasias) is present commonly in hepatic pulmonary and cerebral circulations, demanding knowledge of the risks and benefits of screening and treatment of patients with these complications.

Pathophysiology – Autosomal dominant trait with variable inheritance and penetrance and expression. The clinical manifestations of Osler-Weber-Rendu disease are caused by the development of abnormal vasculature, including telangiectasias, AVMs, and aneurysms. The genetic defect largely involves either one of two genes: ENG or ALK-1. Both of these genes transcribe proteins that are highly expressed on endothelial cells and play important roles in tissue repair and angiogenesis through their common function as receptors for transforming growth factor beta. Defects in the endothelial cell junctions, endothelial cell degeneration, and weakness of the perivascular connective tissue are thought to cause dilation of capillaries and postcapillary venules, which manifest as telangiectasias.

It is believed that in most, it not all, cases, HHT results from endoglin or ALK-1 haploinsufficiency (i.e, lack of sufficient protien for normal function). On basis of theses two genes disease subtype are designated HHT1 and HHT2, respectively.[1-4]

Differing disease patterns in members of same family suggest that other genetic and environmental factor modify the HHT phenotype.

Incidence – The disease is under reported as most of patient unaware of their disease and presenting to wide range of clinicians.

United States - Reported incidence is 1-2 cases per 100,000 populations per year, with a prevalence of 1-2 cases per 10,000 populations. The disease has a clinical penetrance of 97%.

International - The worldwide prevalence is 1 case per 5,000-10,000 population, with a much higher incidence in the Danish island of Fyn, the Dutch Antilles, and parts of France.

Race - Most commonly occurs in white patients, but it has been described in patients of Asian, African, and Arabic descent.

Sex - Equal frequency and severity in both sexes.

Age - Most often presents by the third decade of life but may also be clinically silent.

Diagnosis – International concensus criteria (the Curacao diagnostic criteria) are based on 4 components. The diagnosis is considered definite if 3 criteria are present and is considered possible if 2 criteria are present. The diagnosis is unlikely if fewer than 2 criteria are present. The criteria are as follows:[5,6]

- Spontaneous and recurrent epistaxis
- Telangiectasias - Multiple sites including the lips, oral cavity, fingers, and nose
- Visceral involvement - GI telangiectasia, pulmonary arteriovenous malformations (AVMs), hepatic AVMs, cerebral AVMs, spinal AVMs
- A first-degree relative with Osler-Weber Rendu syndrome according to these criteria.

Clinical Features – The majority of patients with HHT experience only epistaxis, mucocutaneous talengectasia, and iron deficiency anemia secondry to blood loss.

Epistaxis - is the most common manifestation of the disease and occurs in as many as 90% of affected patients. Patients with epistaxis usually present before the second decade of life. Blood transfusions are required in 10-30% of patients, and as many as 50% of patients require surgical treatment.[7,8]

GI tract Bleeding: Recurrent painless GI bleeding occurs in 10-40% of [9,10]

Pulmonary AVMs - Majority of patients with pulmonary AVMs have no symptoms. Only 1/3 of patients show signs of right-to-left shunt through these AVM leading to hypoxemia, cyanosis, and 2ndry polycythemia. [11]

- Complications includes paradoxical embolism, leading to catastrophic events cerebral abscess and embolic stroke and TIA occur in patients with clinically silent PAVMs, carry significant morbidity and mortality, indicating need for early diagnosis and intervention.
- Pulmonary hemorrhage is rare, except in pregnancy (1.4%)

Cerebral AVMs – usually silent 10% of patient experience headache, seizures, ischemia of surrounding tissue due to steal effect, or hemorrhage.[12,13]

MRI is most sensitive non invasive test to screen cerebral AVM though it fails to detect significant proportion of AVM.

Hepatic involvement - Silent involvement occur in 30% of HHT patient. Symptom includes high output heart failure, portal hypertension, hepatic encephalopathy, GI bleed and biliary disease. Large AVMs between hepatic artery and vein cause significant left-to-right shunt with steal syndrome that can cause angina.

AVM between hepatic artery and portal vein leads to pseudocirrhosis of the liver.

Screening for cerebral AVMs- There is controversy regarding screening of asymptomatic individual in different countries. In UK, risk-benefit consideration for asymptomatic cerebral AVM is not considered in favor of treatment as risk of intervention too high for low risk of hemorrhage.[14]

Cerebral MRI is recommended for individual with positive family history of cerebral hemorrhage, or who are symptomatic to rule out aneurysms or AVM.

Management -

Medical Care - Medical and surgical care in patients with Osler-Weber-Rendu syndrome are aimed at decreasing the amount of hemorrhage and minimizing the sequelae of arteriovenous malformations (AVMs), which may develop in multiple organ systems.

Historically, estrogen-related hormones and antifibrinolytic agents have been used the management of bleeding; however, recent studies reveal that their use likely increases the risk of thrombotic events in patients with Osler-Weber-Rendu who have pulmonary AVMs. Because of this finding, patients should receive screening studies for the presence of pulmonary AVMs prior to treatment of the disease.

Novel therapies, such as N-acetylcysteine and tamoxifen (antiestrogenic agent), are also being studied as options for management of recurrent epistaxis in patients with hereditary hemorrhagic telangiectasia (HHT).[15,16] More than 900 respondents from 21 countries are currently included in a study intended to create an epistaxis severity score for use in patients with Osler-Weber-Rendu syndrome.[17]

A case report also illustrates the use of bevacizumab (Avastin) in the treatment of HHT.[18]

Recommendations also advocate the use of antibiotic prophylaxis prior to surgical or dental procedures in all patients with known pulmonary AVMs or positive contrast echocardiography findings. Recent studies also recommend that women with HHT who conceive should be considered to have high-risk pregnancies because of rare major complications and improved survival outcome following prior recognition.[19]

Surgical Care

Septal dermoplasty can reduce the severity of epistaxis by 75%. This procedure is performed by replacing the nasal mucosa with autologous skin grafts. Telangiectasias may also develop on the autologous skin grafts.

Pulsed dye laser treatment may also be used to photocoagulate telangiectasias in the nasal mucosa. As many as 3 subsequent treatments may be necessary before any change in bleeding frequency or severity is observed.

Endovascular embolization for treatment of severe acute epistaxis is also a treatment modality.[20] Patients who undergo endovascular embolization often require repeat embolization and surgical procedures.

Septectomy combined with septal dermoplasty may also be a viable option for patients with severe transfusion-dependent epistaxis.[21]

Embolization of pulmonary AVMs has been shown to be a safe and effective procedure that prevents brain abscess and ischemic stroke if complete occlusion of all pulmonary AVMs is acheived.[22] Embolization is currently recommended for every pulmonary AVM with a feeding artery of 3 mm or more.[23] Other treatment modalities for pulmonary AVMs include surgical ligation.

Life-threatening GI bleeds are often effectively treated by segmental bowel resection.

Embolization of the hepatic artery in selected patients with liver involvement may be used, as well as liver transplantation.[24, 25]

Radiosurgery, microsurgery, or embolization is used to treat cerebral AVMs.

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