Telangiectasias, recurrent epistaxis and a strong family history—a case of Osler-Weber-Rendu Syndrome in Pakistan

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Abstract
Osler-Weber-Rendu syndrome or Hereditary Haemorrhagic Telangiectasia (HHT) is a rare condition, with very few reported cases, especially in Pakistan. As healthcare workers, we encounter multiple cases of recurrent epistaxis in the emergency as well as outpatient departments. However, patients are usually treated symptomatically without a thorough workup. HHT should be considered among the differentials for recurrent epistaxis, as a clinical diagnosis can be made with detailed family history and physical examination. Here is the case of a 58-year-old male who presented to the Gastroenterology OPD, Combined Military Hospital, Lahore, in November 2021, with complaints of generalised weakness and blood in stools. He had a history of recurrent epistaxis and telangiectasias, and further inquiry revealed a strong family history of similar symptoms. He was diagnosed as a case of Osler-Weber-Rendu Syndrome. Informed consent was taken from the patient prior to the writing of the manuscript.

Keywords: Recurrent epistaxis, Telangiectasias, Arteriovenous malformations, Autosomal dominant, Hereditary haemorrhagic telangiectasia.

Introduction
Osler-Weber-Rendu syndrome or Hereditary Haemorrhagic Telangiectasia (HHT) is a rare autosomal dominant genetic disorder. Mutations in the TGF-β superfamily receptor have been identified, as described ahead, and these lead to weakness of endothelial cell junctions and perivascular connective tissue, resulting in dilation of capillaries and post-capillary venules, which manifest as arteriovenous malformations.1 There are two main genetic types of HHT, both known to be caused by heterozygous mutations; four genes have been identified in the pathogenesis. HHT1 involves a mutation ENG (endoglin), which has a predisposition for women and is associated with an increased risk of pulmonary and cerebral arteriovenous malformations (AVMs). HHT2, on the other hand, is associated with a mutation in ACVRL1 (activin A receptor like type 1), also familiarly known as ALK1. This type is associated with an increased risk of liver AVMs. Other mutations that have been identified include GDF2 (growth differentiation factor 2), SMAD4.2 In the United States, the prevalence of HHT was 12.1 per 100,000 persons in 2017; however, data pertaining to this condition is scarce in Pakistan.3

Osler-Weber-Rendu syndrome is characterised by recurrent epistaxis, positive family history, and telangiectasias. Multiple organ systems may be involved; the most common sites include nasal passages, skin and mucosal membranes, liver, gastrointestinal tract, and lungs.4 Severe involvement can lead to septal perforation, liver cirrhosis, portal hypertension, variceal bleeding, severe anaemia due to chronic blood loss, pulmonary haemorrhage, etc.

The Curacao criteria5 provides a guideline for diagnosis based on these clinical features. It mentions epistaxis, family history (first-degree relative with HHT), telangiectasias, and visceral lesions. Based on this, it provides a definite diagnosis if three symptoms are present; possible or suspected diagnosis if two symptoms are present; and unlikely if fewer than two symptoms are present.5

Management is usually done symptomatically; ablative therapies to control nasal bleeds, endoscopic screening of GI bleeds, blood transfusions, and iron replacement for correction of anaemia and vascular embolisation for pulmonary arteriovenous malformations.6 Considering the grave nature of the complications associated with HHT, patients are offered screening for the detection of systemic involvement. Screening guidelines include genetic testing, colon cancer screening, MRI of the brain for detecting cerebral arteriovenous malformations, high-resolution CT scan for pulmonary arteriovenous malformations, and 2D echocardiography, etc.6 In presenting this case report, we aim to broaden the
knowledge base, facilitate better clinical decisions, and ultimately contribute to the timely diagnosis, improved care, and outcomes for individuals affected by Osler-Weber-Rendu syndrome.

**Case Report**

A 58-year-old hypertensive male, a resident of Hafizabad, Pakistan, presented to the Gastroenterology OPD, Combined Military Hospital, Lahore, in November 2021. He complained of new onset darkening of stools and a chronic history of shortness of breath, dizziness, generalised weakness, and loss of appetite. On further inquiry, he had these complaints on and off for the last eight years, however, he had his first episode of melena five days before coming to the hospital. He reported recurrent epistaxis since childhood, also prevalent in his sons and paternal side of the family, suggesting a strong family history (Figure 1). He had a past history of iron deficiency anaemia; however, he had been noncompliant with oral iron therapy.

On examination, his vital signs were within normal limits. There was conjunctival pallor, grade three clubbing, and telangiectasias on the tongue and hard palate. No other cutaneous lesions were observed in the head-to-toe examination. The abdominal and digital rectal examination was unremarkable. The patient was admitted for further management.

Laboratory work revealed that he had severe microcytic anaemia with Hb of 6.5g/dl (normal: 13.5-17.5 g/dl) and MCV of 56.1fL (normal: 80-95 fL), this correlated with a peripheral smear which showed hypochromic, microcytic cells, and an elevated reticulocyte count of 3.2% (normal: 0.5% to 2.5%). An iron profile was ordered as well, which showed a serum iron of 176ug/dL (normal: 50-170 ug/dL) and a serum ferritin of 04 ng/ml (normal: 15-200 ng/ml). Coagulation studies, liver and renal function tests, and stool for occult blood were all within normal limits.

An Upper GI endoscopy, done in 2019, showed one small telangiectasia in the oesophagus but no dilated veins or varices. A repeat endoscopy performed during the current admission showed an increase in the number and size of telangiectasias; one large telangiectasia was observed at the gastroesophageal junction, few telangiectasias were present in the gastric body and one small telangiectasia was seen in the second part of the duodenum; however, no active bleeding was observed (Figure 2). A screening colonoscopy was advised but could not be performed due to an informed refusal by the patient.

![Figure 1: Upper GI Endoscopy showing the presence of multiple telangiectasias.](image1)

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Right upper quadrant Doppler ultrasound to screen for hepatic arteriovenous malformations was done but was normal with no sign of telangiectasias on the liver.

Based on a high clinical suspicion of Osler-Weber-Rendu syndrome a high-resolution CT scan was done which revealed an AV malformation in the upper lobe of the left lung.

2D echocardiography was performed to check cardiac involvement but it was unremarkable and showed normal cardiac functions.

This patient’s recurrent epistaxis, telangiectasias in
multiple organ systems, and a positive family history completed the triad of clinical diagnosis of Osler-Weber-Rendu syndrome, based on the Curaçao criteria. Unfortunately, due to a scarcity of resources and lack of available facilities, a confirmatory genetic test could not be performed on the patient or his family. During his admission, the patient was transfused two units of packed red blood cells and managed conservatively with intravenous fluids and intravenous Omeprazole. He did not have any episode of melena or epistaxis during admission and was discharged with multivitamins, oral iron tablets, and oral Omeprazole.

On monthly follow-ups, he did not report any darkening of stools, nor did he complain of passage of fresh blood via his stools. His weakness had improved; however, he would frequently continue to have episodes of epistaxis for which he was referred to the ENT department for evaluation.

Discussion
Epistaxis is a common presentation in the emergency and outpatient setting and patients are usually managed symptomatically. As healthcare workers, we should keep Osler-Weber-Rendu syndrome in our list of differentials when managing a patient who comes with unprovoked epistaxis, especially when there is a history of recurrence. Other conditions that may present with unprovoked epistaxis include haematologic malignancies like leukaemia, coagulopathies like Haemophilia A and B, von Willebrand Disease, and platelet disorders like autoimmune thrombocytopenia. These may be screened for and subsequently ruled out by a complete blood count with differential and a coagulation profile.7

Telangiectasias, on the other hand, may be seen in conditions such as Ataxia-Telangiectasia, among others. However, they may be ruled out on the basis of clinical features; neither our patient, nor his family members exhibited ataxia, and they did not have any features that may have indicated immunodeficiency (i.e. recurrent infections).8

Thus, if a timely diagnosis is made, further complications related to HHT can be avoided and morbidity can be significantly reduced. However, because of the rarity of the condition, it is often missed and it still remains under-reported in Pakistan.9 Brain abscess, stroke, anaemia due to chronic gastrointestinal bleeding, high output cardiac failure, portal hypertension, liver cirrhosis, pulmonary haemorrhage, and septal perforation are among the grave complications associated with Osler-Weber-Rendu syndrome.1

Once diagnosed as a case of Osler-Weber-Rendu Syndrome, appropriate investigations should be performed to screen for potential complications. Pulmonary arteriovenous malformations can be screened by thoracic CT or contrast echocardiography. Cerebral arteriovenous malformations may be identified by MRI of the brain or more accurately by MR Angiography. Upper GI endoscopy should be performed, especially when there is a history of anaemia or GI bleeding and a Doppler ultrasonography can screen for hepatic AV malformations.10 To date, there is no consensus on the best approach for the management of HHT, and, therefore, treatment should be tailored according to the requirements of the patient. Management should be focused on supportive and symptomatic care and prevention of complications.10

Conclusion
Osler-Weber-Rendu syndrome is a rare condition and can prove to be a complicated disease, although it can be diagnosed with a good clinical history and thorough general physical examination. Owing to the varied modes of presentation and complex symptomatology, it can be a challenge to diagnose. Therefore, a high suspicion should be kept especially when there is a positive family history of unprovoked bleeding episodes. Once diagnosed, management is mostly conservative, focusing on symptomatic treatment, but has far-reaching effects on the prevention of complications. Furthermore, counselling for genetic disorders and screening strategies should be employed and a holistic approach to the management of the disease should be employed.

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Authors’ Contributions

**MMAS, TH:** Collected case history and physical examinations, follow-up, manuscript review, write-up and formatting.

**RUD:** Supervised the junior doctors, involved in inpatient care, writing of the manuscript, revision.