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Case Report

Hereditary hemorrhagic telangiectasia associated with acrofacial vitiligo

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Abstract Hereditary hemorrhagic telangiectasia (HHT) or Osler Weber Rendu syndrome is an autosomal dominant systemic vascular dysplastic disorder presenting with telangiectases over the skin and arterio-venous malformations (AVMs) in internal organs.[1] Mutations in Endoglin (ENG or CD 105) and Activin receptor-like kinase 1 (ACVRL1 encoding the ALK1) genes of the TGF β are responsible for HHT1 and HHT2 respectively.[1] They account for the majority of HHT cases. Mutations in MADH4 (which encodes for SMAD4 protein, a transcription factor that mediates signal transduction in the TGF-β pathway) result in juvenile polyposis with HHT syndrome (JP-HHT).[1,2] Bone morphogenetic protein (BMP9 or GDF2)[3] genes also showed pathogenic mutations. Drosha mediated micro RNA biogenesis contributes significantly to the control of vascular development and homeostasis by TGF β.[3] Loss or reduction of the Drosha function may predispose carriers to HHT.
HHT is associated with autoimmune diseases like lupus erythematosus, scleroderma, primary biliary cirrhosis, thyroiditis, vitiligo and, platelet dysfunctions like primary thrombocythaemia, and with recurrent iridocyclitis and myelodysplastic syndrome. We report the third case of HHT associated with acrofacial vitiligo.

Key Message Diagnosing a case of HHT is crucial as the patients and their asymptomatic first-degree relatives with HHT must be screened for the presence of undiagnosed AVMs, and early preventive measures have to be started to prevent delayed complications. We present here the third case showing association of HHT with acrofacial vitiligo.

Key words
Hereditary hemorrhagic telangiectasia, Osler-Weber-Rendu syndrome, Acrofacial vitiligo.

Introduction

Hereditary hemorrhagic telangiectasia (HHT) or Osler Weber Rendu syndrome is an inherited autosomal dominant disease with an incidence of 1 in 5000 and high penetration by middle adulthood.[1] It is characterized by telangiectases and AVMs, which are high-flow lesions that result from an abnormal direct arterial-to-venous connection.[1] Arterio-venous malformations had been found in the brain, lung, gastrointestinal tract, and liver. Herein we present a case of HHT with epistaxis and acrofacial vitiligo. As per our knowledge, the association of HHT with acrofacial vitiligo had been reported in two cases till now. Hence, this is the third case of HHT with acrofacial vitiligo.

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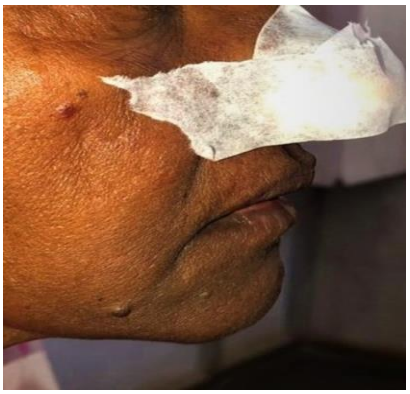
Case history

A 50-year-old woman with epistaxis presented to the Dermatology department with complaints of white patches over both feet, left leg, and lips for 15 years. She has had recurrent episodes of epistaxis for 12 years. There was a history of blood transfusion 2 years back. A history of similar complaints in two first degree and one-second degree relatives was also present. Her younger sister died five years back due to excessive bleeding, further details of which are not known.

On examination, multiple telangiectasias were present over both cheeks **(Figure 1 & 2)**, left auricle, one each over the front and back of the upper trunk. In oral mucosa, they had been present over the dorsum of the tongue, hard palatal mucosa **(Figure 3)**, upper and lower lips. Each telangiectasia was 2-5mm in size with or without a slight elevation. Purpuric macules were present over the palmar aspect of distal phalanges of 2nd to 5th left fingers **(Figure 4)** and plantar aspect of both great toes, right 4th toe, and right middle fingernail. Splinter hemorrhages were present over a few fingernails.



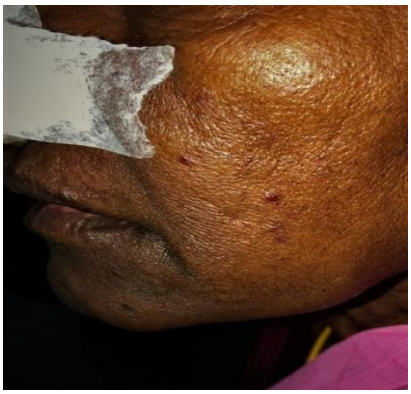


Figure 1 & 2 Telangiectatic papules are visible on the right and left cheeks. A nasal pack secured for epistaxis can be seen.

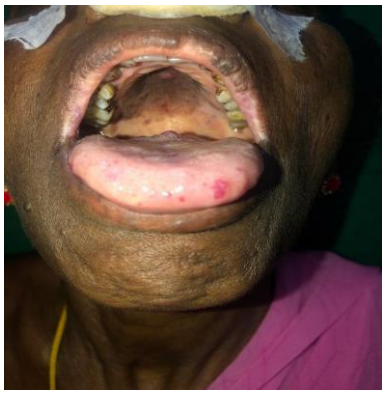


Figure 3 Multiple telangiectasias are visible on the dorsum of the tongue and hard palatal mucosa. Depigmented macules can be seen over the upper labial mucosa.

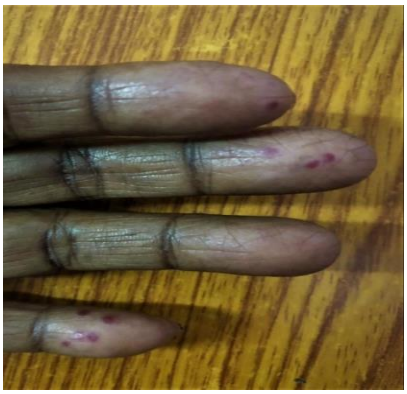


Figure 4 Multiple telangiectatic macules are visible over the palmar aspect of distal phalanges.

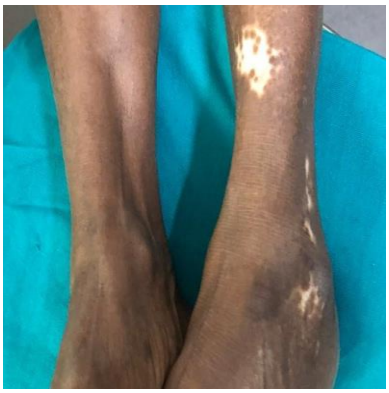


Figure 5 Depigmented macules with follicular and marginal repigmented spots are visible on the left lower leg and lateral malleolus.

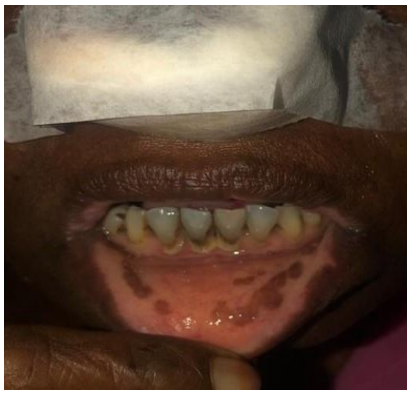


Figure 6 Depigmented macules with spontaneous follicular repigmentation spots can be seen over the lower labial and the gingival mucosa.

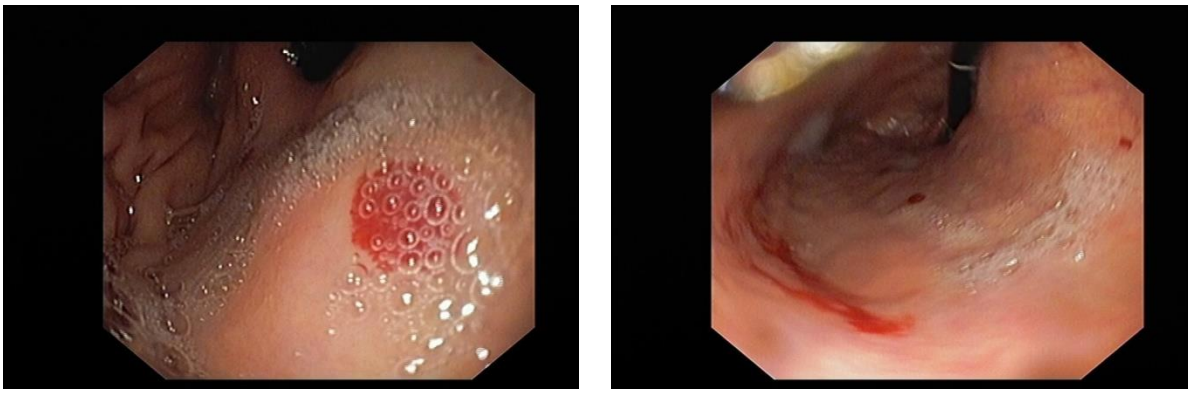


Figure 7 Sub-epithelial telangiectatic spots are visible over the fundus and body of the stomach on upper gastrointestinal endoscopy.

She also had well defined depigmented patches over the left lower leg **(Figure 5)**, left medial and left lateral malleoli, right leg, right lateral malleolus. Upper **(Figure3)** and lower labial **(Figure 6)**, gingival and right and left buccal mucosae were involved.

Pallor and icterus were present. An ejection systolic murmur was heard.

The diagnosis of HHT associated with acrofacial vitiligo was made clinically, based on the history and physical examination findings.

Cavernous malformation of the portal vein were seen in the ultrasound abdomen and telangiectasias were noticed in the stomach gastrointestinal endoscopy **(Figure 7)** had been found on further investigation.

Her hemoglobin was 9.4g%, packed cell volume-27% (36-46% is normal), mean corpuscular volume - 68fl (83-101 fl is normal), mean corpuscular hemoglobin - 23.7 pg (27-32 pg is normal), mean corpuscular hemoglobin concentration - 34.9 g/dL (31.5-34.5 g/dL is normal). Peripheral smear showed dimorphic anemia. The remaining parameters in hemogram were normal. Complete urine examination and serum iron were normal. Serum ferritin was decreased (6.29ng/ml (female- 13-232ng/ml is normal). Serum bilirubin – 2.2mg/dl (0.2-1.0 mg/dl is normal). Serum albumin–2.6mg/dl (3.3-4.5mg/dl is normal). The liver function tests and renal function tests were normal. Stool for occult blood was negative. Viral markers were negative.

Discussion

Hereditary hemorrhagic telangiectasia (HHT) is a rare mesenchymal vascular dysplasia resulting in visceral AVMs and smaller mucocutaneous telangiectasias. HHT can be diagnosed on basis of Curaçao criteria[4] viz., 1) Spontaneous, recurrent epistaxis, 2) Multiple telangiectasias at specific sites (lips, oral cavity, fingers, nose) 3) Visceral malformations such as gastrointestinal telangiectasias, and AVMs of the lung, brain, and liver 4) Family history: a first degree relative with HHT. Diagnosis of HHT is definite if three criteria are present, possible if two are present and unlikely if fewer than two are present. This case fulfills all of the four diagnostic Curaçao criteria. Hence, a definite diagnosis of HHT had been made in this case.

Epistaxis is the most common and usually the first symptom occurring due to telangiectasias inside the nose. This case, too, had epistaxis as the first symptom. Pentraxin 3 level[5] is elevated in HHT and reflects the severity of disease-associated epistaxis. This patient developed anemia due to epistaxis.

Telangiectasias occur in up to 75% of cases with onset typically in childhood and increases with age. This case telangiectasias located mainly over the oral mucosa and also over hands, feet. This distribution follows the published studies.[1]

This case is compelling because of the association between Osler-Weber-Rendu syndrome and vitiligo. As far as we knew, this is the third case of HHT associated with vitiligo with two previous reports[6,7] having similar associations.

Vitiligo in all three cases was of more than ten years duration, and it is of acrofacial type in all of them. The association of HHT with vitiligo could be a coincidental association due to a common chromosomal link (chromosome 7) for both vitiligo and HHT.[8,9] Endoglin is produced by endothelial cells commonly and by activated monocytes in HHT. Endoglin is the product of one of the gene implicated in the pathogenesis of HHT. Thus, HHT and vitiligo could be related to the same molecular abnormality that affects a primitive germ cell.

As per the latest data, dysregulated angiogenesis is one of the factors leading to the pathogenesis of HHT and the vascular endothelial growth factor (VEGF), may have a role in this disease, by altering the angiogenic-angiostatic balance in the affected tissues. Hence, antiangiogenic therapies that target the abnormal vessels and restore the angiogenic-angiostatic balance are candidates for the treatment of HHT.

Bevacizumab[2] is a recombinant humanized monoclonal antibody and an antiangiogenic agent that blocks angiogenesis via VEGF inhibition. It appears to be promising in HHT as an intravenous formulation for reducing the frequency and severity of epistaxis. Pazopanib[10] is a tyrosine kinase inhibitor taken by mouth that blocks VEGF receptors and has emerged as a promising systemic therapy in reducing bleeding complications, but it is not curative. Other therapies include anemia correction, antifibrinolytics, and hormonal treatment.[2]

Treatment of HHT requires a multidisciplinary approach of dermatology, cardiology, pulmonology, hematology, interventional radiology, ear nose, and throat (ENT), hepatology, and genetics.

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