Recurrent Epistaxis and Purple Vascular Stains in an Elderly Patient

Dear Editor,

Hereditary hemorrhagic telangiectasia (HHT) is an inherited disorder of the vasculature characterized by a plethora of manifestations, including recurrent epistaxis and cutaneous and visceral arteriovenous malformations (AVMs). The disease originally described by Rendu, Osler, and Weber about a century ago was initially thought to be a form of hemophilia. Later, it was described as a separate entity with distinct pathogenic mutations and dominant mode of inheritance.

A 66-year-old woman from Kashmir valley presented with four years duration of recurrent spontaneous nosebleeds and numerous purplish stains over her face and acral skin. She was a known hypertensive for many years, controlled on telmisartan. There was no significant family history. On examination, there was the presence of multiple red-purple telangiectatic papules with slightly rough surface. They were predominantly distributed over the acral areas of fingers and toes, over the nail bed, lips, face, ear helices, and over the mucosal surface of the oral and nasal cavity [Figures 1-3]. She had no other systemic symptoms.

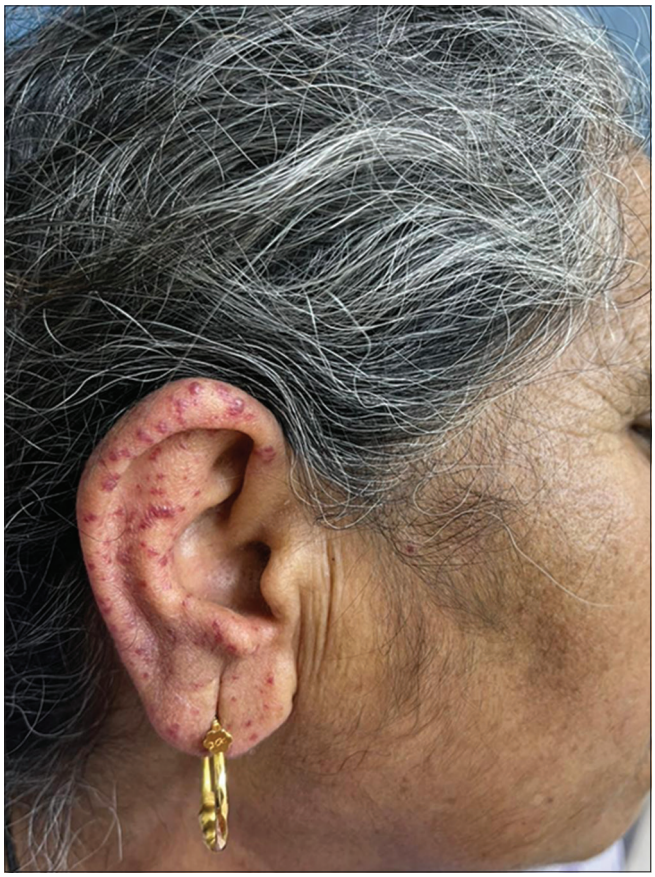

Figure 1: Multiple pinhead sized telangiectasias over ear pinna

Her magnetic resonance imaging (MRI) with angiography of the brain showed no significant abnormality. The stool for occult blood was negative and her chest and abdominal radiographs revealed no abnormality. Based on the Curacao criteria,[1] she was diagnosed as a case of possible hereditary hemorrhagic telangiectasia. Due to relatively late age of onset and a negative family history, and in the absence of fulfillment of all diagnostic criteria, a confirmatory genetic testing was done. Whole exome sequencing revealed a heterozygous missense variation in exon 7 of the (activin receptor like kinase 1) *ACVRL1* gene (chr12:g. 51916218C>T) that results in the amino acid substitution of tryptophan for arginine at codon 425 (p.Arg425Trp). The patient was given supportive management in the form of tranexamic acid for recurrent epistaxis and counselling was done regarding the disease prognosis.

Osler-Weber-Rendu disease, also called as HHT, is a rare genetic disorder of vessels characterized by mucocutaneous and gastrointestinal telangiectasias associated with AVMs in various organs, including lungs, central nervous system, and liver. Family history is present in 70% of cases and this is attributed to the autosomal dominant mode of inheritance.[2] Epistaxis is one of the most striking and earliest symptoms present in 96% of cases, which usually appears in childhood at the age of around 10–11 years.[2,3] This is followed by the appearance of mucocutaneous telangiectasias, which become apparent later when patients are in their third or fourth decade of life.[3,4] It has been estimated that 70% of affected individuals have manifestations by 16 years of age

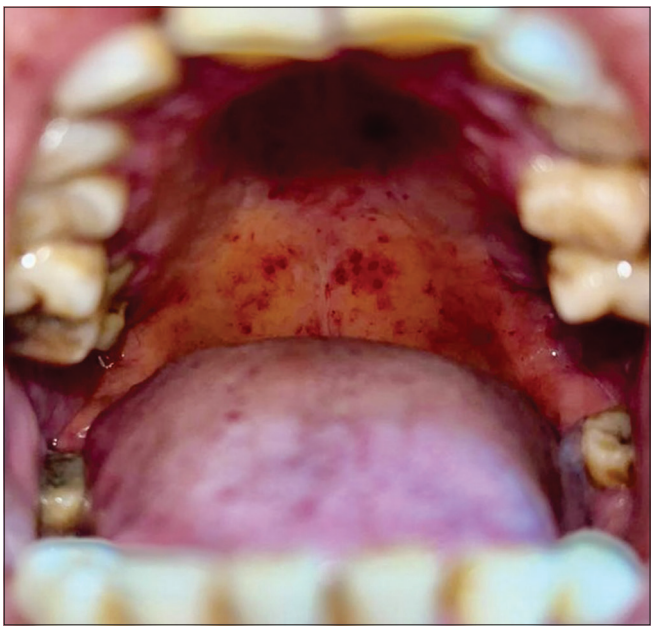

Figure 2: Mucosal telangiectasias over palate

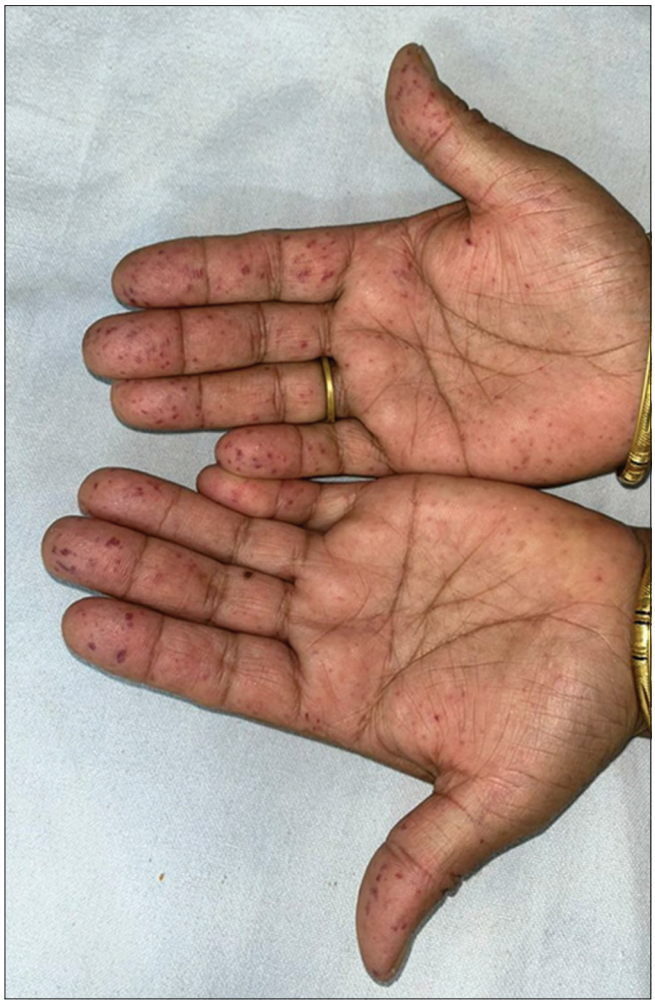

Figure 3: Multiple purplish telangiectasias over hands

and around 90% manifest by 40 years of age.[3] Our patient had a late onset of disease in her sixties and there was no family history. This can be due to sporadic mutations or non-recognition of the disease in affected parents.

The disease occurs most commonly due to mutations in pathways involving transforming growth factor beta (TGF-β) leading to dysplasia of vessels. The most studied mutations include those in the endoglin (*ENG*) gene on chromosome nine, characterized in HHT subtype 1, and in the activin receptor-like kinase 1 (*ACVRL1)* gene on chromosome 12, characteristic of subtype 2.[3] Both of these are transmembrane proteins bound to TGF-β in endothelial cells and they play an important role in angiogenesis and vasculogenesis. Thus, these mutations result in defective vessel walls leading to increased fragility and consequent turbulent flow.[3] The index case had mutations in the *ACVRL1* gene with R411W variation, which has been reported in patients with phenotype of HHT 2. Functional studies have shown that this missense change causes lack of response to BMP9 (bone morphogenetic protein 9) stimulation and protein mislocalization, disrupting ACVRL1 protein function.[5]

The presence of cutaneous telangiectasias is observed most frequently over the lips, nose, cheeks, tongue, ears, hands, and wrists. Internal organ involvement occurs most commonly in the form of GIT (gastrointestinal involvement) in 13%–30% of patients who present with occult GIT bleeds.[6] Other internal organs involved include hepatic AVMs, pulmonary involvement, and cerebral involvement. Diagnosis is established on the basis of consensus Curacao criteria,[1] which includes the presence of epistaxis, mucocutaneous telangiectasias, positive family history, and visceral fast flow lesions. The presence of three or more criteria makes it a definite case, while the presence of two or more criteria makes it a possible case of HHT. The management is largely symptomatic and involves the multidisciplinary management of iron deficiency anemia, iron supplementation, oral tranexamic acid, and ablative therapies for mucocutaneous telangiectasias in the form of electrofulguration and carbon dioxide laser. Recently, the role of anti-angiogenic therapies like bevacizumab, an anti-VEGF (vascular endothelial growth factor), has been postulated, but the cost and monitoring are limitations.[7] At the end, genetic counselling of such patients is of utmost importance with regular follow-up and screening of children for possible development of symptoms.

To conclude, HHT is a rare genetic disorder which should be suspected by a dermatologist in any patient of any age presenting with severe epistaxis and mucocutaneous telangiectasias, even in the absence of family history and internal organ involvement.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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We thank the patient for granting permission for clinical photography. A written informed consent was taken.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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