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Hereditary Hemorrhagic Telangiectasia in a Sickle Cell Trait Patient: A Report of a Rare Case with Use of Nuclear Medicine, and a Literature Review

Authors' Contribution:

Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

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Conflict of interest: None declared

Patient: Female, 49-year-old
Final Diagnosis: Hereditary haemorrhagic telangiectasia
Symptoms: Anemia • dyspnea • epistaxis • lipothymia • melena • weakness
Medication: —
Clinical Procedure: Electrofulguration
Specialty: Gastroenterology and Hepatology • Genetics • Radiology

Objective: Rare disease
Background: Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is a rare autosomal dominant disease.
Case Report: Here, we report a case of a 49-year-old Brazilian woman with a history of multiple hospitalizations, sometimes life-threatening anemia, and uncommon clinical manifestations.
Conclusions: We provide a brief literature review regarding the most common signs and symptoms, history, diagnosis, and treatment. Special attention is given to the techniques for identifying hemorrhagic areas, to the presence of angiodysplasia in gastric tissue, and the identification of sickle cell trait, this being an unprecedented hematological condition in the presentation of the disease. Thus, further studies on the relationship between sickle cell trait and the syndrome are needed.

MeSH Keywords: Anemia • Anemia, Iron-Deficiency • Sickle Cell Trait • Telangiectasia, Hereditary Hemorrhagic

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Background

Hereditary hemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant disease with variable penetrance, but in 20% of cases it originates from sporadic mutations. This syndrome makes blood vessels after the capillary bed thin and vulnerable to injury due to changes in the elastic lamina and muscle layer [1,2]. Thus, it is marked by multiple cutaneous vascular malformations in mucous membranes and/or internal organs, vascular malformations affecting the lungs, brain, spinal cord, gastrointestinal tract, and liver, and are often associated with complications [3–5]. It affects both sexes and all ethnic groups [4,5]. The prevalence varies widely by region, with the highest rate in the Afro-Caribbean population of the Netherlands Antilles, reaching 1: 1331, while the worldwide prevalence ranges from 1: 5000 to 1: 8000 [3].

HHT manifests mainly as epistaxis, which is the most common symptom (more than 90% of cases) [1,6]. Mucocutaneous telangiectasias in digital pulps, lips, and oral and nasal mucosa are also frequent symptoms, occurring in about 80% of cases, in addition to the possibility of involvement of other organs, such as pulmonary arteriovenous malformations (AVMp). Furthermore, hepatic vascular and central nervous system malformations occur [1,7]. AVMp are present in about 10–30% of cases, being strongly indicative of the disease, since the majority of cases of AVMp (50–80%) correspond to HHT [6,8]. Most patients develop gastrointestinal bleeding at some point in life [1,3]. These digestive hemorrhages, as well as epistaxis, are important causes of chronic iron deficiency anemia in patients with HHT.

According to the gene involved in the disease, HHT can be classified into HHT1 or HHT2. The HHT1 subtype is associated with a mutation in the Endoglin gene that encodes the receptor of the same name accessory to TGF β , and which is located on chromosome 9 (9q 33–34 or OWR-1). The subtype HHT2 is due to a mutation in the ACVRL1 gene, located on chromosome 12 (12q11–14 or OWR-2), responsible for encoding the ALK-1 receptor for TGF β [1,9]. HHT1 is more linked to AVMp and cerebral arteriovenous malformations, while HHT2 tends to affect the liver tissue and the spinal cord, and these malformations are almost only caused by the HHT2 genotype [1,10].

The diagnosis of HHT2 is made according to criteria published in 2000 by the Scientific Advisory Board of the HHT Foundation International, Inc., known as the “Curaçao Criteria”. This scoring system uses 4 findings as a basis for diagnosis: recurrent epistaxis, multiple telangiectasias (on lips, oral cavity, fingers, and nose), visceral lesions such as gastrointestinal telangiectasias (with or without bleeding), pulmonary, hepatic, cerebral, spinal arteriovenous malformations, and family history with at least 1 first-degree relative with the disease. The definitive diagnosis is made when at least 3 of these criteria are present.

The diagnosis is possible or suspected with only 2, and if less than 2 criteria are present, the hypothesis of HHT is discarded [11]. The presentation of these criteria depends on age, since the individual develops more symptoms throughout life [4].

There is no consensus on the best treatment for this rare syndrome; therefore, palliative treatment is provided [12]. It is necessary to avoid blood transfusions and hospitalizations as much as possible, in addition to maximizing quality of life. Each patient should be evaluated individually to assess the relative benefits of each method [9].

Case Report

A 49-year-old Brazilian woman came to the Emergency Service complaining of lipothymia, muscle weakness, dyspnea, palpitations, epistaxis, and melena recurring for about 1 month. Clinical stabilization and blood transfusion were performed. On physical examination, she was found to have marked pallor and apparent telangiectasias on exposed skin and oral mucosa. She reported having episodes of epistaxis since childhood, beginning at 9 years old, and sporadic bleeding, most common in the left nostril, triggered or intensified by exertion and/or stress. The hematology and gastroenterology teams, given the clinical criteria of Curaçao and genetic test results, diagnosed the patient with HHT1. However, during this investigation of the patient's frequent bleeding and anemia, hemoglobinopathies were also investigated through hemoglobin electrophoresis, in which sickle cell trait was identified. Epistaxis was treated with cauterization of the hemorrhagic focus, and the patient was advised to maintain humidification of the nasal mucosa.

The patient returned 4 years later presenting an upper-gastrointestinal hemorrhage. Esophagogastroduodenoscopy and colonoscopy were performed, which indicated the presence of gastric and colon angiodysplasias, treated with electrofulguration (EF) with a bipolar catheter. In the following year, another hospitalization was necessary due to dyspnea, asthenia, epistaxis, severe anemia, and precordial pain. At the time, a pulmonary arteriovenous fistula was identified and promptly treated by an endovascular approach (Figures 1, 2). Eleven years after the diagnosis was made, a chest tomography was suggestive of congestive heart failure, with venous overload, and ascites and pleural and pericardial effusion, due to the common vascular malformations of the disease.

Since then, the patient has been treated in the Emergency Department due to successive cases of gastrointestinal bleeding (duodenal bulb, cecum, transverse colon, ascending colon) always treated by EF, in addition to complementary treatment with transfusions and iron supplementation. In her last hospitalization, the laboratory evaluation exposed life-threatening

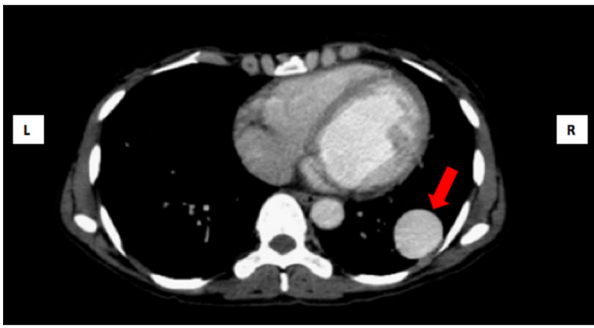


Figure 1. Computed tomography image in the arterial phase showing arteriovenous fistula (red arrow).

anemia with hemoglobin of 2.7 g/dL, hematocrit of 9.8%, and ferritin of 3.5 ng/mL. Transfusion and subsequent treatment with intramuscular iron replacement were initiated.

Discussion

This disorder was first described by Sutton in 1864, then Rendu differentiated the disease from hemophilia by publishing a report of a 52-year-old man with recurrent epistaxis and telangiectasias on the face, torso, lips, tongue, and soft palate. Thus, Rendu speculated that the epistaxis resulted from nose injuries. Rendu also noticed similar symptoms in other family members (the patient's mother and brother had copious epistaxis).

In 1901, Sir William Osler again described the familial pattern of the disease, but went further, when he perceived the visceral involvement of the disease, identified at autopsy. In 1907, Weber presented a clinical description in a paper containing a series of cases. Two years later, Hanes proposed the term "hereditary hemorrhagic telangiectasia"; however, the name Rendu-Osler-Weber syndrome survived [13,14].

Anemias in general can be classified according to their intensity into mild, moderate, severe, or life-threatening, according to the US National Cancer Institute, and levels below 6.5 g/dL are considered life-threatening [15]. Although there are indications that HHT can trigger iron deficiency anemia, the occurrence of severe and life-threatening anemia due to this disease is rare [6,16,17]. Thus, it is believed that epistaxis and chronic blood loss from the gastrointestinal tract are the most likely mechanisms involved with anemia developed by these patients [16,18].

Epistaxis, telangiectasias, and frequent gastrointestinal bleeding (with angiodysplasias) are factors of great importance for understanding our patient's severe anemic conditions. All are known mechanisms of chronic blood loss that lead to iron deficiency anemia; however, the presence of sickle cell trait (SCT) may represent a hemolytic component given the associated conditions of the patient, even though SCT is considered a benign condition [1,15].

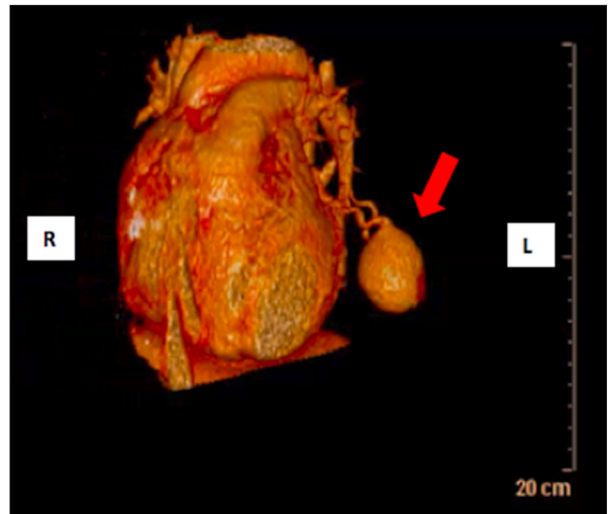


Figure 2. 3D reconstruction of the arteriovenous fistula (red arrow), made from computed tomography images, to program the surgical approach.

After all, although it is not considered a disease and is usually asymptomatic, some studies show that SCT is not as indolent as most people think; it is associated with venous thromboembolic events in adverse situations or after strenuous exercise, rhabdomyolysis, ischemia/splenic infarction, glaucoma after eyeball injuries, and renal medullary carcinoma [19]. Under extreme conditions, such as high altitude, severe dehydration, or very high-intensity physical activity, erythrocytes may become deformed. However, in our patient no signs of hemolysis were identified and lactate dehydrogenase and bilirubin levels were normal. Still, it is important to recognize that the description of cases of patients with HHT associated with SCT is rare in the literature, with no cases related to this phenotype in the SciELO and PubMed databases.

It is also worth mentioning the role of some complementary exams in the evaluation of gastrointestinal bleeding from HHT. Along with the more well-known esophagogastroduodenoscopy and colonoscopy, we highlight the role of nuclear medicine, since, through scintigraphy, it was possible to show signs of hemorrhage in the cecum and ascending and transverse colon (Figure 3). Even though it was not possible to specify the exact foci of the hemorrhage, it was possible to guide the choice of the most appropriate tests; in this case, a colonoscopy.

Conclusions

In conclusion, we present a rare genetic disease, HHT1, or Rendu-Osler-Weber syndrome, associated with sickle cell trait, as well as frequent episodes of life-threatening anemia and infrequent findings such as angiodysplasias. This report is expected to guide medical teams in the management of this rare syndrome, to provide strategies to identify bleeding, and

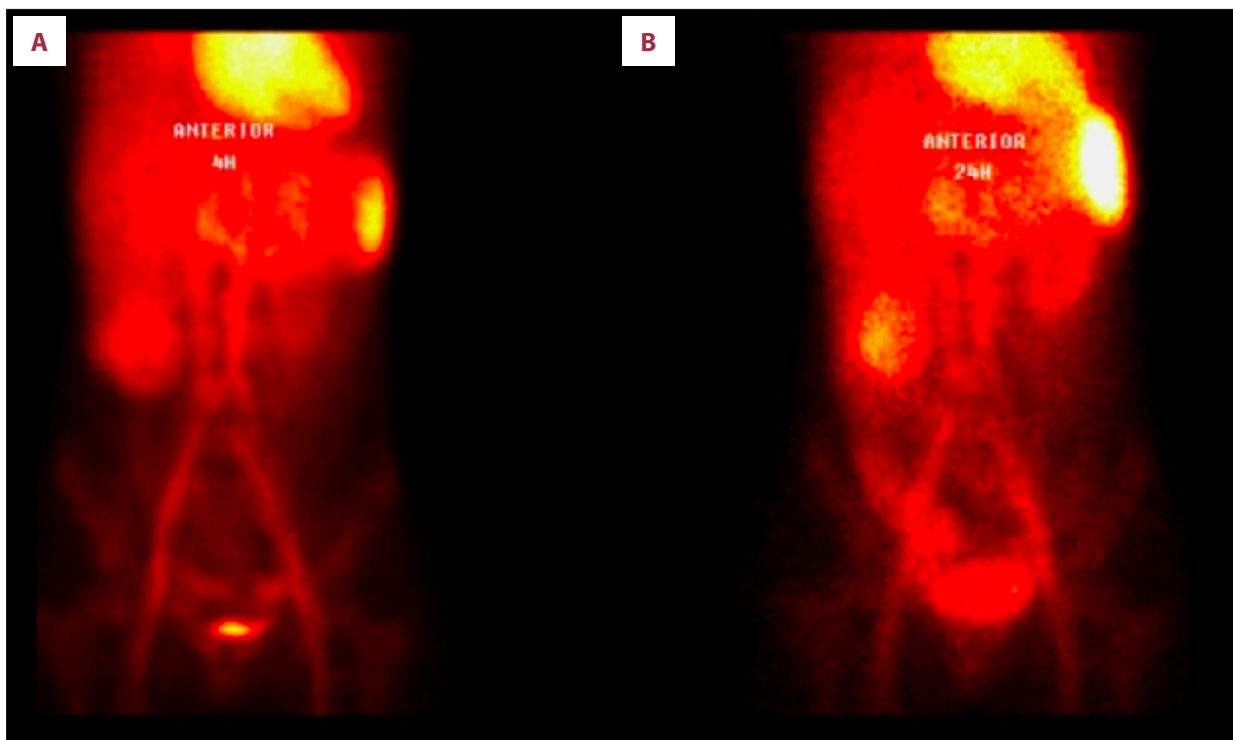


Figure 3. Scintigraphy images revealing an accumulation of radiotracer (Technetium- pyrophosphate -99m-labeled red blood cell) in the topography of the cecum (B), ascending colon, and transverse colon (A, B) in the late images, compatible with gastrointestinal bleeding.

to raise awareness of the possible associated factors that can aggravate the already known manifestations of HHT. Further studies are needed to define the relationship between sickle cell trait and the pathological presentation of this syndrome.

Conflict of interest

None.

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