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The Importance of a Multidisciplinary Approach in a Patient with Long-term Multisystemic Manifestations of Unrecognized Hereditary Hemorrhagic Telangiectasia

Vesna Sredoja Tišma[1], Ana Vlašić[2], Petar Gulin[2], Renata Huzjan Korunić[3]

[1]Dermatovenerology Unit, Dubrava University Hospital, Zagreb, Croatia. [2]Department of Otorhinolaryngology and Head & Neck Surgery, Dubrava University Hospital, Zagreb, Croatia. [3]Clinical Department of Diagnostic and Interventional Radiology, Dubrava University Hospital, Zagreb, Croatia.

Corresponding author:
Vesna Sredoja Tišma, MD
Dubrava University Hospital,
Zagreb, Croatia
vesna.tisma@mail.inet.hr

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ABSTRACT Hereditary hemorrhagic telangiectasia (HHT), also called Rendu-Osler-Weber syndrome, is a rare autosomal dominant multisystemic vascular disorder, characterized by widespread mucocutaneous teleangiectasias, frequent visceral arteriovenous malformations (AVM) and a tendency for bleeding. This diagnosis should be suspected in all dermatological patients with generalized mucocutaneous vascular lesions at sites of predilection, associated frequent epistaxis and a positive family history. The aim of this paper is to emphasize the importance of a multidisciplinary approach, the role and timely cooperation of dermatologists and otorhinolaryngologists in the early clinical recognition and diagnosis of the disease. We present a family case of a 63-year - old patient with typical clinical features of HHT and long-standing multisystemic complications of unrecognized disease.

KEY WORDS: hereditary hemorrhagic teleangiectasia, multidisciplinary approach, multisystemic manifestations

INTRODUCTION

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant, multisystemic vascular dysplasia with mucocutaneous telangiectasias, angiomas, frequent visceral arteriovenous malformations (AVM), and a tendency towards bleeding. The most commonly used synonym for HHT is Rendu-Osler-Weber syndrome, an eponym based on the names of physicians Osler, Rendu, and Weber, who each independently described the disease.

The estimated worldwide disease prevalence rates are between 1:5000 and 1:10 000, depending on the ethnic group studied (1), with approximately 85,000 individuals affected in Europe (2) and 1,4 million people worldwide (1).

HHT is a heterogeneous disorder divided into two clinically indistinguishable forms: HHT-1 caused by mutations in endoglin (ENG) gene mapping on chromosome 9q (3), and HHT-2 caused by mutations in A receptor like kinase 1 (ALK1) mapping on chromosome 12q (4). More than 600 mutations causative of HHT have been identified on the molecular level (5). Pathogenic mutations cause a disturbance of the balance between pro- and antiangiogenic signals necessary for normal vascular development (6).

The diagnosis of HHT requires the presence of at least three of the four clinical criteria. These so-called Curaçao criteria (5) include recurrent epistaxis, mucocutaneous telangiectasia, visceral AVM, and positive

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family history of HHT in a first-degree relative. The Curaçao clinical criteria have a good diagnostic performance (1). Patients who have 3 or 4 criteria definitely have HHT, and clinical diagnosis in such patients is relatively simple. However, not all patients have this triad or tetrad of symptoms and HHT cannot be easily or quickly diagnosed in such cases. Those patients who meet 2 criteria may have HHT, and those with 0 or 1 criterion are unlikely to have HHT (2). Genetic testing can be helpful in those patients with a possible clinical diagnosis of HHT (2).

Symptoms develop with increasing age (1). Most patients only experience manifestations of epistaxis, mucocutaneous telangiectasias, gastrointestinal bleeding, and iron deficiency anemia (1). Epistaxis is usually the first clinical manifestation. Because epistaxis is a very common symptom in the general population, episodes of night epistaxis are more specific for diagnosis of HHT (7). Vascular mucocutaneous lesions usually appear after the first episode of epistaxis (1). They most frequently present on the face, lips, nose, tongue, auricles, fingertips of the hands, and trunk (8). The International HHT Foundation has reached a consensus that the diagnosis of HHT requires the presence of telangiectasias on at least 3 of the typical previously mentioned localizations (9). Dermoscopy is a simple, non-invasive method for detecting microscopic mucocutaneous vascular lesions in patients affected by HHT. The dermoscopic pattern and distribution of telangiectasias, age at their onset, and associated features are useful for distinguishing HTT from different vascular skin disorders or different hereditary syndromes similar with similar symptoms. In most cases, cutaneous telangiectasia and angiomas are asymptomatic. LASER therapy can be considered for cosmetic reasons and in rare cases of painful lesions.

The appearance of this vascular disorder appear together with abnormal vascular shunts (AVM) in the internal organs such as the lungs, liver, or brain, is responsible for more serious systemic manifestations of the disease. Mucosal telangiectasias located in the gastrointestinal tract are more serious because they can lead to severe internal bleeding and consequently to severe iron deficiency anemia, which can sometimes be a life-threatening condition and require transfusion and/or interventional procedures.

The main goal of management is to maximize the number of patients receiving effective prevention

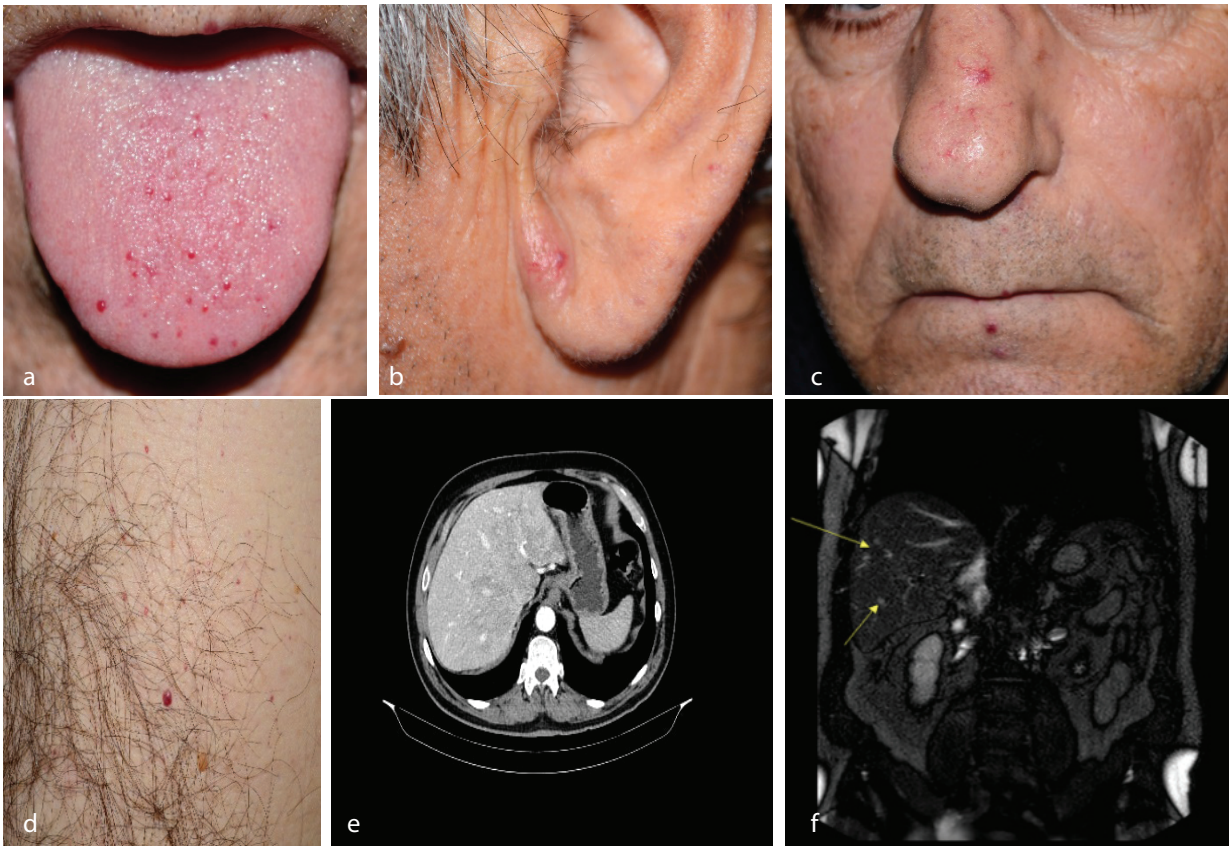

Figure 1. Numerous telangiectatic lesions and angiomas in a 63–year old male patient with HHT on the ear (a), tongue (b), nose and lips (c), trunk (d). MSCT showed suspicious vascular lesions in the liver (e). MR examination confirmed AV shunts in the liver (f).

strategies, in order to limit the number and severity of HHT complications (2).

CASE REPORT

In 2016, a 63-year-old man was repeatedly admitted to our emergency internal medicine clinic due to severe anemia after referral by his family physician. He reported increased fatigue, repeated massive nosebleeds, and dark stool, as he was taking iron supplements due to anemia. His medical history included high blood pressure and diabetes type 2. Laboratory tests on admission at the end of December 2016 showed anemia (Hgb 78 g/L; Htc 0.258 L/L; MCV 74.1 fL; MCH 22.4 pg; MCHC 303 g/L; RDW 20.1%; E 3.48 ×10 12 /L; Trc 350×109 /L; MPV 7.8 fL. Note: hypochromia, anisocytosis). Renal function, liver function, glycemic levels, and electrolytes were within normal range. Angiomatous changes in the skin and visible mucosa of the oral cavity (Figure 1, a, b, c) were not described in the physical status at the time. A chest X-ray showed a tortuous descending course of the thoracic aorta. The patient was subsequently given 2 doses of erythrocyte concentrate, and further gastroenterological (GE) diagnostic procedures and gastroenterological and otorhinolaryngological (ORL) examination were proposed.

In early January 2017, a suspected liver lesion was observed on an abdominal ultrasound, while esophagogastroduodenoscopy showed a suspicious vascular formation about 1 cm in size on the gastric mucosa and total colonoscopy revealed internal hemorrhoids (grade 1). Epistaxis recurred during this GE diagnostic procedure, and the patient was referred to an emergency ORL clinic. A multislice computed tomography (MSCT) scan of the abdomen was also recommended.

ORL examination performed in mid-January 2017 revealed numerous crusts and telangiectatic changes on the mucosa of the nasal septum and oral mucosa. The patient reported frequent epistaxis episodes occurring since 1982. There was also positive family history, as his mother also had frequent epistaxis. The otorhinolaryngologist suggested dermatological consultation for an evaluation of the observed numerous angiomatous changes on the skin and on the oral cavity mucosa.

Dermatological examination performed at the end of January 2017 revealed numerous telangiectatic lesions and angiomas of highly variable size involving the ear (Figure 1, a), nose and lips (Figure 1, c), arms, neck, trunk (Figure 1, d), and fingertips. Physical examination of oral mucosa revealed telangiectatic changes on the lips and tongue (Figure 1, b). Given the number, clinical appearance, and characteristic localization of angiomatous skin changes, involvement of the oral mucosa (tongue), positive family history (epistaxis and similar skin changes in his mother and daughter), associated recurrent epistaxis and chronic microcytic anemia, the dermatologist confirmed the suspicion of the otorhinolaryngologist regarding HHT. The patient was also advised to take photoprotection and to avoid mechanical irritation of

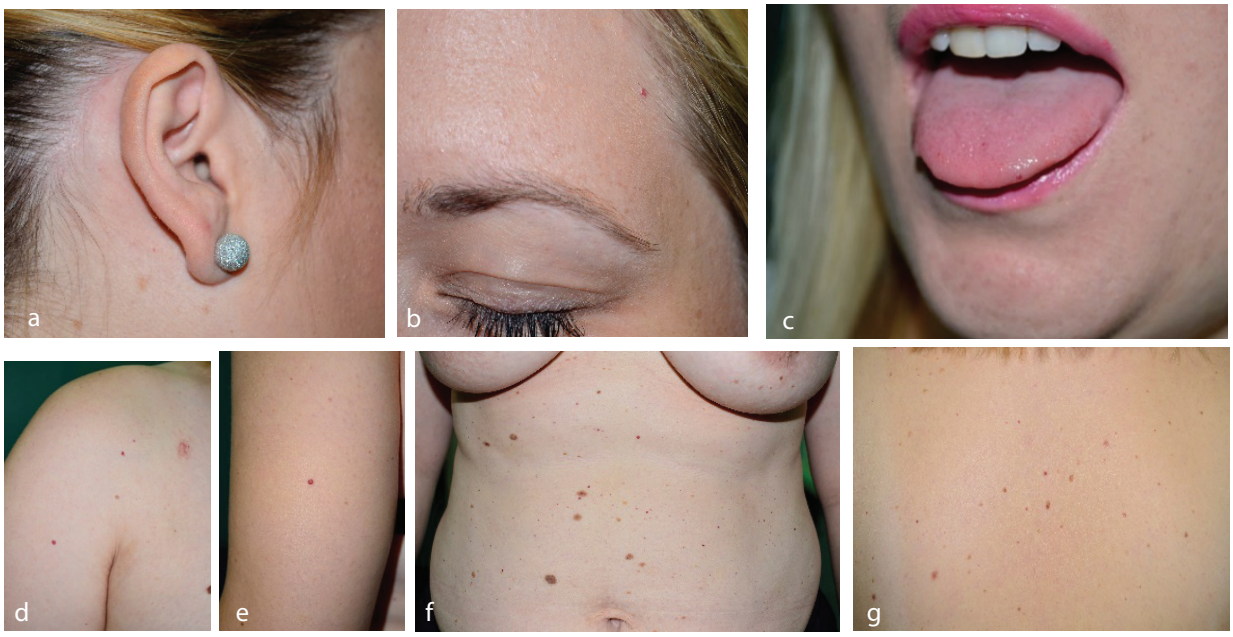

Figure 2. Telangiectatic lesions and angiomas of various sizes, on the tongue (a), forehead (b), ear (c), arm (d), right shoulder (large, arborising teleangiectasias) (e), trunk (f) and upper portion of the back (g) in the patient's 34-year-old-daughter with HHT.

numerous angiomatous changes (if possible). The option of LASER therapy for cosmetic reasons was also explained to him.

In early March 2017, the patient was readmitted to an emergency internal medicine clinic due to severe anemia after being referred by his family physician (with the latest laboratory findings Hgb. 60 g/L; MCV 63.6 fL attached) and once again received a transfusion (2 doses of erythrocyte concentrate).

Subsequent MSCT scans of the abdomen in mid-March 2017 showed hypervascular lesions in the liver, 7 and 8 mm in size (Figure 1, e) and abdominal magnetic resonance (MR) imaging performed in early December 2017 confirmed numerous AV shunts in the liver (Figure 1, f).

In late December 2020, a urologist examined the patient for erythrocyturia (5-10 E in urine sediment) and established a working diagnosis of erythrocyturia, without recording erythrocyturia as a symptom of the previously established diagnosis of HHT. Further urological diagnostic procedure (cytologic examination of the urine sediment and urinoculture) was recommended.

In the meantime, in October 2018, at the initiative and collaboration of otorhinolaryngologist and dermatologist, the patient's 34-year-old daughter was diagnosed with HHT based on 3 of 4 established Curacao criteria being positive, as follows: 1) recurrent epistaxis in the last 5 years; 2) mucocutaneous telangiectasias and angiomas at typical sites (Figure 2); and 3) a positive family history of HHT in her father and grandmother. Screening procedure for AVM (MSCT scans of the thorax, abdominal ultrasound and MR of the brain) performed in 2019 showed no signs of arteriovenous fistulas or AVM. Due to low levels of iron and ferritin, a hematologist recommended the introduction of peroral iron with vitamin C into therapy.

DISCUSSION

HHT is still often misdiagnosed because many physicians are not familiar with its various associated symptoms and clinical manifestations, which range from minimal to life-threatening (10). Therefore, specialized centers have been developed worldwide in recent years that provide a multidisciplinary approach involving all physicians who are specialized and trained in all aspects of HHT (10).

Due to the lack of appropriate comprehensive multidisciplinary teams in Croatia and the unavailability of genetic testing or sending samples to referent HHT centers for all patients, there are no accurate data on the number of patients with HHT. In our view, appropriate comprehensive multidisciplinary teams should include family physicians, otorhinolaryngologists (ORL), dermatologists, hematologists, gastroenterologists, pulmonologists , neurologists, urologists, radiologists, doctors of dental medicine, geneticists, and other specialists as required, depending on individual cases. Establishing such cooperation of different specialists is needed as soon as possible to facilitate timely diagnosis of HHT.

We have presented the case of a patient who had to wait 36 years from the onset of symptoms until the diagnosis of HHT, although he had a typical tetrad of symptoms and met all 4 Curacao criteria for establishing a definitive clinical diagnosis of HHT. During these years, he visited several doctors of different specialties. Numerous complications greatly affected his quality of life. Most physicians in this case did not recognize the varied symptoms and signs as a single disease but concentrated on resolving problems related to their specialty. Family history was positive, and the patient's mother also had frequent epistaxis whereas the daughter had epistaxis and similar skin lesions. In the meantime, after a physical examination by a dermatologist and otorhinolaryngologist and following current recommendations, HHT was also diagnosed in the patient's daughter. Based on these criteria, we concluded that three members of three generations in this family represent cases of HHT.

The aim of this paper is to emphasize the importance of a multidisciplinary approach and the role and collaboration of otorhinolaryngologists and dermatologists in early clinical detection and diagnosis of this disease, since epistaxis and angiomatous mucocutaneous changes are the first symptoms and main manifestations of HHT. These symptoms also appeared first both in the case of our patient, who had a long-standing unrecognized disease, and in the case of his daughter.

Widespread telangiectasias and angiomas, the first visible presentation of HHT, are very common in everyday dermatological practice. Dermatologists should be aware of the importance of carefully examining the visible mucosa in all dermatological patients with multiple angiomas and telangiectasias on the skin and talking to those patients about recurrent epistaxis and family history of similar skin changes and bleeding problems.

From a dermatological perspective, the most important differential diagnosis is a very similar and also rare autosomal dominant disorder – hereditary benign telangiectasia (HBT). In contrast to HHT, HBT is a disorder without mucosal involvement and without a tendency towards bleeding (11).

Advancements in understanding the molecular genetics of HHT have made it possible to identify many associated gene mutations, thus facilitating the classification of family members at being at risk of the disease. However, until genetic testing becomes available at all centers worldwide, imaging techniques represent the only essential support to clinical data for identifying individuals affected with HHT and detecting those visceral vascular malformations that may require treatment (10). Timely diagnosis is therefore crucial to prevent disease-related complications and offer genetic counselling to families (1).

CONCLUSION

Due to the wide range of systemic clinical manifestations and low prevalence of the disease, a multidisciplinary approach is needed to avoid misdiagnosis or failure to recognize the disease for a long time, which can have serious, sometimes life-threatening complications.

Only a holistic multidisciplinary approach with the collaboration of all physicians who are specialized in all aspects of HHT and which is based on talking to patients about their medical and family history and symptoms, careful physical examination, and looking for typical signs of HHT on the skin and mucosa, enables successful screening of patients with HHT.

This disease should always be kept in mind when considering differential diagnosis in patients with numerous mucocutaneous telangiectasias and angiomas, recurrent epistaxis, episodes of internal bleeding, and microcytic anemia.

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