

Rendu-Osler-Weber Syndrome: A Case Report

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Abstract

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Hereditary hemorrhagic telangiectasia (HHT) or Rendu-Osler-Weber syndrome, is a rare genetic disorder with autosomal dominance and variable penetrance. The typical findings of the disease are telangiectasias in skin and mucous membranes, and arteriovenous malformations presenting in the organs like lung, intestine, brain and liver. It is characterized by the classic triad of recurrent epistaxis, mucocutaneous telangiectasias and visceral hemorrhages, with familial occurrence.

This article describes a case of HHT of an adult patient, associated with multiple angiodysplastic injuries in the nasal mucosa, upper gastrointestinal tract, lungs and who presents continuous blood loss, resulting iron deficiency anemia. Based on clinical and diagnostic findings, we diagnosed this case as HHT, which has rarely been reported in our literature.

Introduction

Manifestations of the hereditary hemorrhagic telangiectasia (HHT) were first described in 1896, when Henri Jules Louis Rendu described for the first time the classical picture of HHT as a disease of mucocutaneous telangiectasias, epistaxis, and familial nature. The following decade brought accurate case descriptions of the disease by William Osler (1900) and Frederick Parkes Weber (1907), so the eponym "Rendu-Osler-Weber" was created [1].

Although the first description was made more than a century ago, only in the last decade the real confirmation of the genetic origin of disease has been proven. HHT is a disorder with autosomal dominant inheritance and variable penetrance, although in some the cases there is no family history and they could represent sporadic mutations [2, 3]. HHT also exhibits

the property of "incomplete penetrance", an inability to express the full spectrum of disease phenotype, despite carrying a defective gene [4]. In earlier studies the prevalence of the disease was estimated at 1 in 100,000, however, HHT prevalence nowadays is more frequent than formerly thought [5, 6]. The vascular malformations in HHT consist of direct arteriovenous connections through thinwalled aneurysms, and range from small telangiectases (predominantly mucosal, skin, and visceral) to larger visceral arteriovenous malformations (AVM) [6]. Most clinical complications of the disease are related to pulmonary AVM (PAVM) about 30-60% [4, 7, 8]. It is estimated that 11-40% of HHT patients have gastrointestinal, 8-16% hepatic, and 5-11% cerebral involvement [1, 9]. Epistaxis is usually the first manifestation up to 90% of the patients [5, 6].

The present study describes a typical case of HHT of a 47-year-old female, which is manifested by recurrent epistaxis, multiple angiodysplastic injuries presenting in the organs and had been suffering from iron deficiency anemia.

Case report

A 47-year-old woman had a history of admissions to the Department of Hematology, Clinical Center Kragujevac, due to recurrent mild manifestations of iron deficiency anemia from 1991 to 2011. The clinical description of the patient reveals that the frequency of hospitalization increased in the last two years decurrent of the persistence of anemia. Despite a high-dose oral iron replacement regimen, her hemoglobin levels did not reach normal values. She continued to present sporadic episodes of dyspnea, hypotension, tachycardia, headaches, weight loss, which had been observed without any medical intervention. In December of 2011, the patient invariably presenting with these symptoms, followed by low hemoglobin level 47 (116-154 g/L), and decreased levels of hematocrit 0.2 (0.345-0.463 L/L), ferritin 12 (20-300 $\mu\text{g/L}$), serum iron 2.5 (6.6-26 $\mu\text{mol/L}$) and platelet count 76 (158.7-387.7 $\times 10^9/\text{L}$). Blood laboratory findings demonstrated severe iron deficiency anemia.

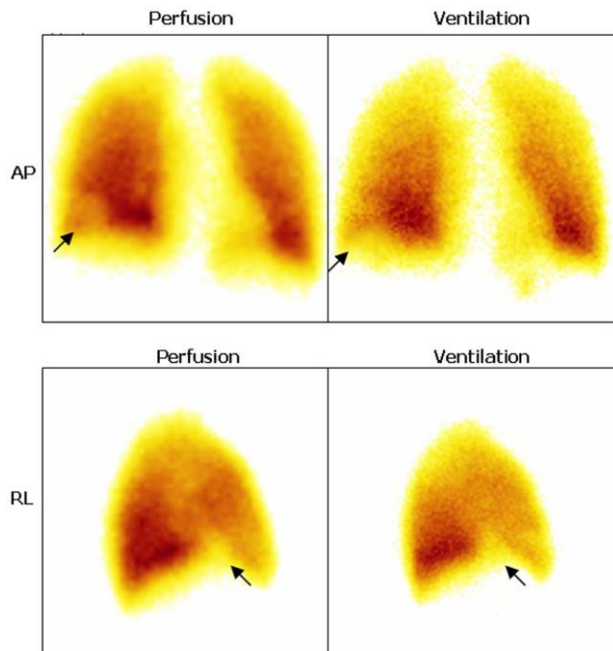


Figure 1: Radionuclide ventilation/perfusion lung (V/P) scanning, using radiopharmaceuticals $^{99\text{m}}\text{Tc-DTPA}^*$ (aerosol)/ $^{99\text{m}}\text{Tc-MAA}\dagger$; * diethylenetriaminepentaacetic acid (DTPA) labelled with metastable nuclear isotope of technetium-99; † macro aggregates of human albumin (MAA), labelled with metastable nuclear isotope of technetium-99.

She was admitted to hematology clinic and instituted therapeutical support under demand. Patient has been treated with blood transfusions and getting

hemodynamic stabilization after the treatment replacement with concentrated erythrocytes. Other laboratory work-up was normal, including normal coagulation profile and stool occult blood test (Adler-Weber). Although there was no clear history of low dietary intake of iron, evaluation for a source of bleeding or a malabsorptive process was initiated. During her cutaneous examination, at ear-nose-throat clinic, pallor and discoloration in the oral mucosa and tongue was noticed without any telangiectasias. Anterior rhinoscopy revealed haematic dots and crusts on septal mucosa.

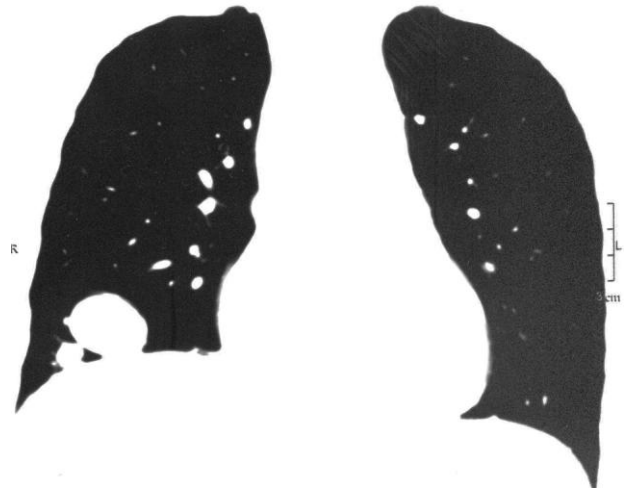


Figure 2: Multisliced computed tomography (MDCT) of the chest (coronal section) in lung parenchyma invert window, show sharply defined lobulated soft tissue mass of uniform density in the lower lobe of the right lung.

Endoscopy of the upper digestive tract was performed. The results of the endoscopy indicated multiple gastric angiodysplasias of the fundus and body of the stomach and paraesophageal hiatus hernia as well. Fiberoptic rectosigmoidoscopy disclosed any angiodysplastic injuries in the superior and medial portions. The routine chest radiograph revealed a defined lobulated area of uniform density in the lower lobe of the right lung. The patient was submitted to ventilation-perfusion (V/P) scintigraphy. Images that were obtained, in SPECT modality, revealed non-segmental perfusion defects in the lower right hemitorax with corresponding defects in the ventilation scan (Figure 1). Although there was no evidence of "ventilation-perfusion mismatch", the diagnosis of pulmonary embolism was ruled out, but may provide evidence of other pathologies, like neoplasma or PAVM. Regarding all previous aspects, we assumed the existence of PAVM.

Next, multislice computed tomography (MDCT) of the chest was indicated. The lesions on the MDCT chest were identified as subpleural, nodular, lobulated mass (35 x 30mm) of uniform density in the right lower lobe anteriorly (Figure 2), with a single feeding artery and a draining vein, consistent with PAVM (Figure 3). Computed tomographic (CT) study

of the skull did not found evidence of AVMs, although it revealed a small area of supratentorial subcortical calcification.

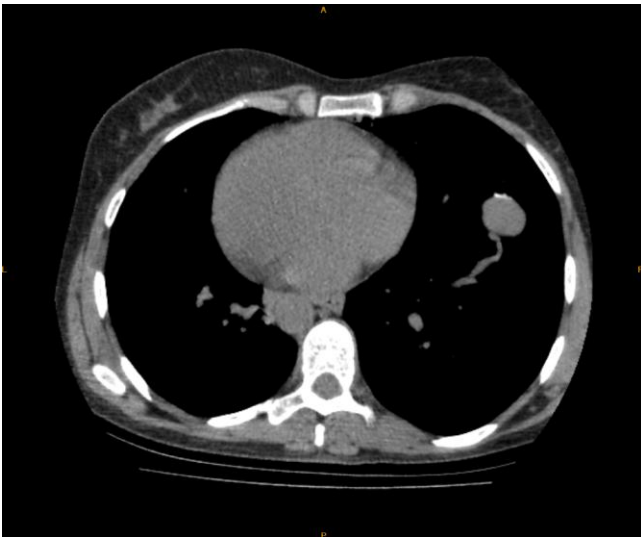


Figure 3: Multisliced computed tomography (MDCT) of the chest (axial section) in soft tissue window, showing lobulated mass of uniform density in the right lower lobe anteriorly, with a single feeding artery and a draining vein.

Discussion

The prevalence of HHT was estimated at 1–2 in 100,000, with a regional variations, homogeneous race and gender distribution, and areas of high prevalence such as in the Netherlands Antilles (1:1,331), in the Danish island Funen (1:3,500), in Vermont USA (1:16,500), and in northern England (1:39,216) [8, 10]. From a genetic standpoint, average prevalence is more frequent (about 1:10,000) characterized by incomplete penetrance [4-6].

The term "hereditary hemorrhagic telangiectasia" was first used in 1909 [6], but the real confirmation of the genetic origin of disease has been only proven a century later. HHT represents autosomal dominant disease, caused by mutations in one of two genes that have led to its subclassification into types HHT1 and HHT2 [11]. Type 2 is more frequent.

Genes, endoglin on chromosome 9q34 and the activin receptor-like kinase 1 on chromosome 12q13 [4, 12], encode for transmembrane proteins involved in the transforming growth factor (TGF)- β signalling pathway. Expressed genes are predominantly on vascular endothelium [3], and may explain abnormalities in vasculogenesis and angiogenesis [13, 14]. Additionally, a HHT type 3 has been described [2]. At least two more loci (and yet unidentified genes) seem to be involved in patients with HHT [2, 13, 15].

The exact pathologic mechanisms that underlie HHT pathogenesis remain obscure, though they are presumably a result of genomic mutations.

The development of a cutaneous telangiectasia is a progressive process. In the early stage a focal dilatation develops, and in a more advanced stage the venules, arterioles and their branches are markedly dilated. Such dilation makes the capillaries disappear after some time, causing the arteriovenous malformations [4, 12].

Data from the personal history of the patient revealed repeated episodes of nasal bleeding of unknown cause, multiple episodes of recurrent palpitations, a fatigue, dizziness in recent decades but without physician's involvement. These abnormalities have been described in the literature, according to which, by the age of 16 years, 71% of affected individuals develop some sign of HHT, rising to over 90% by the age of 40 years [10]. Recidivant nosebleed, result from telangiectasia of the nasal mucosa, is the most common clinical characteristic of HHT, up to 90% during infancy, and are often misdiagnosed [11]. Other clinical finding of small mucosal and skin telangiectasias is present at 13-89% [11]. Our patient's disease severity varied from severe to such mild manifestations, that the disease is never suspected. Only when the routine chest radiograph revealed a soft tissue mass in the lower lobe of the right lung, which was confirmed, after V-P scan and chest MDCT, as PAVM. According to recent studies, the incidence of the PAVM was estimated up to 50-60% of persons with HHT [15, 16]. PAVM appear in both lungs, having a predilection for the lower pulmonary lobes, rather multiple [35–65%] than solitary [6]. Such case was at our patient too. PAVM are mostly without hemodynamic or hematological alterations during infancy [7]. Symptoms start around the second decade of life and may include cyanosis (18%), hemoptysis (10%) and chest pain (6%) [15]. These conditions, which may lead to hypoxemia, dyspnea and especially iron deficiency anemia, are often clinically misdiagnosed [10]. Possibly severe or lethal hemorrhagic complications have been described in about 7% patients with HHT and PAVM, including intrabronchial or intrapleural rupture of PAVM with ensuing hemoptysis or hemothorax [15]. PAVM also result in direct right to left shunts, so the absence of a filtering capillary bed, allow embolism to reach the systemic arteries and can lead to neurologic complications including transient ischemic attack, cerebral stroke and cerebral abscess [16, 18]. Cerebral involvement of HHT occurs in 5–11% of patients with HHT [9]. Investigations using CT of the patient's skull didn't found evidence of AVM, but calcification was noted which can lead to minor intracranial hemorrhage. Gastrointestinal (GI) AVM occurs in 11-40% of the patients, and can lead to GI bleedings, and are more commonly situated in the stomach or duodenum than in the colon [6, 16, 18]. We also detected angiodysplasias in the bulbus and the duodenum of the patient. Multiple episodes of iron deficiency anemia at our patient could be a result of intermittent GI hemorrhage. Fiberoptic rectosigmoidoscopy didn't reveal any angiodysplastic injuries, and

stool occult blood was also negative. Hepatic involvement is rare, present in 8%-16% of the patients with HHT [14, 18], including portal hypertension and hepatocellular insufficiency [5, 6, 8].

HHT is increasingly diagnosed in children especially since genetic testing has been made available [3, 7, 15]. All persons with a family history of HHT should undergo genetic screening, because about 12% of those affected may develop clinical symptoms [3]. Owing to the lack of genetic diagnosis in routine clinical practice, initial diagnosis should rely on the targeted physical examination, especially for its potential for associated morbidity. The manifestations may not be present at birth, but develop with increasing age [10, 11] Due to late onset penetrance, the diagnosis is usually missed. Diagnosis is based on the four components of the "Curaçao" criteria, established by the Scientific Advisory Board of the HHT Foundation International, Inc. (Table 1) [12, 19]. The current clinical diagnosis of HHT requires that at least 3 out of 4 criteria should be fulfilled in order to confirm the diagnosis. Our case met three of four criteria: recurrent epistaxis, telangiectasias, GI bleeding combined with anemia. Assessment of the family history was unobtainable, because family information was unclear and without any medical record.

Table 1: Diagnostic criteria for the diagnosis of HHT (Curaçao criteria).

Criteria

1. Spontaneous epistaxis and recurrent nasal bleeding
2. Telangiectasia multiple and in characteristic sites (lips, oropharynx, fingers and nose)
3. Visceral lesions-gastrointestinal, pulmonary, hepatic, brain and spinal arteriovenous malformations
4. Family history-one first degree relative with HHT

HHT diagnosis

- Definite: 3 or more criteria present
Possible: 2 criteria present
Unlikely: < 2 criteria present

The current diagnostic approach includes CT scan which is now the gold standard for the diagnosis of AVM. Chest CT-scan, especially with intravenous injection of contrast medium, enables the differential diagnosis of PAVM from other nodules and assessment of perfusion [20]. Pulmonary angiography is usually used for transcatheter treatment, and for CNS involvement magnetic resonance imaging is the best diagnostic method [7, 8]. Pulse oximetry with arterial blood gas analysis and V/P scan are not widely in use, however, V/P scan can be useful for quantifying a shunt fraction in a patient with PAVM [21]. From these findings, the diagnosis of hereditary hemorrhagic telangiectasia, at our patient, was made.

Therapeutic approach is of palliative nature

only and helps prevent complications. There still is no consensus on the best treatment option, so multidisciplinary collaborative approach is required [1, 23]. In patients with epistaxis, multiple approaches have been tried, including electrocautery, septo-dermoplasty, embolization [6, 9]. In recent years, the process of catheter embolization for PAVMs and GI bleeding has been enforced, although there are still no studies regarding the long term follow up of these patients [22]. Hepatic AVM's are currently treated only if patient show a signs of liver and heart failure [5,8]. New therapy approaches is now available including thalidomide and a recombinant, humanized, monoclonal antibody Bevacizumab. Although the overall outlook is promising, the real efficacy of these treatment approaches still needs further evaluation [23, 24].

In conclusion, more than once in this study, we emphasized that greater clinical awareness may be the first step to identify patients with HHT, and may play a key role in the timely referral of these patients. Unfortunately, as is the case at our patient, clinical manifestations are often under-recognized and the diagnosis and treatment are frequently delayed for many years, even decades. Thus, it is fundamentally important that the physician be up to date to the disease's etiopathogenesis to perform correct diagnosis, alter the clinical course and affect the outcome. In the management of the disease, especially in high-risk individuals, it is advised to suspect presence of the most serious complications such as PAVM, respiratory distress and lethal hemorrhagic complications.

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