Case Report

Dyspnea with anemia turned out to be a case of hereditary hemorrhagic telangiectasia

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Abstract:

Hereditary hemorrhagic telangiectasia (HHT) is a rare autosomal dominant inherited disorder of the vascular system. It can be asymptomatic but when symptomatic most common presentation being epistaxis. It can involve any organs of the body like lungs, skin, liver brain, GI mucosa etc. We are reporting a case of HHT presented to us with dyspnea and severe anemia. He had arteriovenous malformations of different visceral organs and telangiectasia of skin along with presence of similar history in first-degree relatives.

Key words:

Anemia, arteriovenous malformation, dyspnea, hereditary hemorrhagic telangiectasia

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Introduction

Hereditary hemorrhagic telangiectasia (HHT), also known as Osler–Weber–Rendu syndrome, is a rare autosomal dominant fibro vascular dysplastic disorder of the vessels characterized by development of multiple abnormal vessels.[1-3] It is characterized by development of multiple characteristic telengiectasia in skin and mucous membrane associated with formation of arteriovenous malformation (AVM) in organs like lung, brain, intestine, liver etc.[1-5] Here we report a case of HHT who came to us primarily for evaluation of anemia with progressive dry cough and shortness of breath. At first a diagnosis of pulmonary AVM was suspected on the basis of chest radiology which led to further workup and a final diagnosis of HHT was reached.

Case Report

A 40-year-old male was admitted with complain of progressive fatigue and shortness of breath for the last 2 years. On enquiry, he gave history of recurrent epistaxis from childhood which increased in frequency and severity for the last 2 years with absence of hemoptysis. He had history of blood transfusions on two occasions during the last 2 years. He had recent onset of blurring of vision without any double vision in his left eye for 2 months. On physical examination, moderate pallor along with clubbing was found. Complete hemogram revealed hemoglobin (Hb%)–4.3 g/dl (normal value 14–18 g/dl), total leukocyte count–7400/μl (normal value 4000–11000/μl), mean corpuscular volume (MCV)–80 fl (normal value 83-97 fl), mean corpuscular hemoglobin concentration (MCHC)–26 g/dl (normal value 32–36 g/dl), erythrocyte sedimentation rate (ESR)–25 mm/h in the first hour (normal value 0–15 mm in the first hour), and platelet count–480,000/μl (normal value 150,000-450,000/μl). Peripheral blood smear examination showed microcytic and hypochromic red blood cells. Other laboratory investigations were serum ferritin 10 μg/l (normal value 50–200 μg/l), serum iron 23 μg/dl (50–150 μg/dl), transferrin saturation 8% (normal value 30–50%), and total iron binding capacity (TIBC) 440 μg/dl (normal value 300–360 μg/dl). Serum electrophoresis revealed normal hemoglobin pattern. Hematological workup and iron profile findings were suggestive of iron deficiency anemia. Tests for the coagulation profile revealed clotting time (CT)–100 seconds (normal value 90–130 seconds), bleeding time (BT)–5 minutes (3–7 minutes), prothrombin time (PT) – 12 seconds (normal value 10–14 seconds), and activated partial thromboplastine time (APTT) – 28 seconds (normal value 21–35 seconds). Chest x-ray of the patient revealed a peripheral based mass in the right lower zone. CT scan thorax with contrast showed a peripherally based lung mass with suspected abnormal vascular communications radiating toward hilum. CT angiography of thorax confirmed the diagnosis of pulmonary AVM by the presence of two AVM with anterior one being larger and posterior one being smaller [Figure 1]. Echocardiography with saline contrast media revealed micro bubbles in left atrium within four cardiac cycles of their appearance in right atrium, indicative of intrapulmonary shunting and absence of intracardiac shunting. On dermatological examination, numerous telangiectatic vessels were noted in lips, under the surface of tongue, ear lobules, nail beds, and palm [Figure 2]. Nasal endoscopic examination revealed multiple bleeding spots along with presence of numerous

telangiectatic vessels in both septum and turbinate [Figure 3]. Stool was tested positive for occult blood. On upper gastrointestinal (GI) endoscopy there was presence of telengiectatic vessels in various parts of GI mucosa with absence of varices (stomach, first part of duodenum) although not as numerous as that of nasal mucosa. Fiber optic-bronchoscopic examination revealed numerous telangiectatic vessels in both wall of trachea and bronchus. Ophthalmological examination also showed numerous telengiectatic vessels in conjunctival mucosa and presence of hemorrhage in macula of left eye possibly resulting from rupture of telengiectatic vessels in retina. On the other hand, no abnormality was detected in CT and MRI of brain. A liver function test revealed total bilirubin 0.8 mg/dl (normal value 0.2–1.4 mg/dl), AST 15 U/l (normal value 7–21 U/l), ALT 20 U/l (normal value 5–40 U/l), alkaline phosphatase 42 U/l (normal value 32–110 U/l), and albumin 4.5 g/dl (normal value 3.5–5 g/dl). Ultrasonography and CT scan with contrast of abdomen did not reveal any vascular abnormality. At this point, our differential diagnosis was hereditary hemorrhagic telangiectasia, capillary malformation-AVM syndrome, CREST syndrome, etc. Screening of family members was done in the form of complete history, physical examination (nasal and oral mucosa examination), chest radiography, and arterial blood gas testing (with measurement of the shunt fraction). On family history, epistaxis was present in first-degree relatives like mother and one brother [Figure 4]. Nasal endoscopic examination was done in his mother and his brothers and it revealed telengiectatic vessels in nasal septum and turbinate of mother and one brother. So, a diagnosis of hereditary hemorrhagic telengiectasia was made. Two units of blood transfusion were done to correct his anemia and favorable response regarding his dyspnea was observed immediately. Laser therapy was performed for the telangictatic vessels of his skin, nasal mucosa and gastrointestinal tract. Pulmonary AVM was treated by surgery as the feeding artery was less than 3 mm. The patient was discharged and asked for annual visit with complete blood count and tests for occult blood in stool.

Discussion

Pulmonary AVMs are abnormal vascular structures that provide a direct capillary-free communication between the pulmonary and systemic circulation.[2] Approximately 50–85% of pulmonary AVMs are associated with HHT.[6] On the other hand 15–35% of individuals with HHT have pulmonary AVM in association.[6] In all patients having pulmonary AVMs a careful search has to be made for diagnosis of HHT so that it is not missed. A detailed family

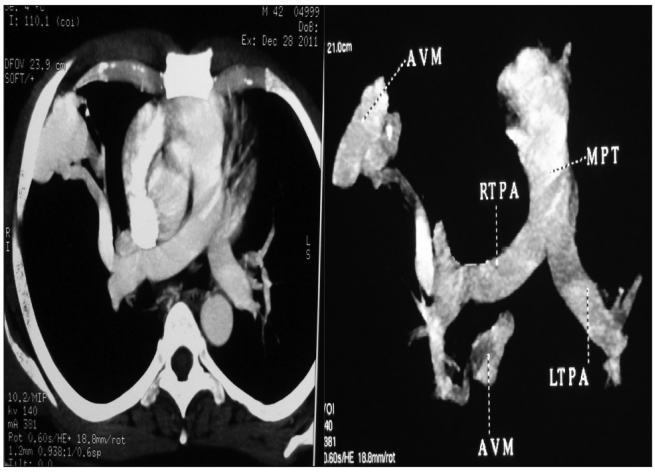

Figure 1: CT angiography of thorax showing two pulmonary AVM, anterior one being larger and posterior one being smaller

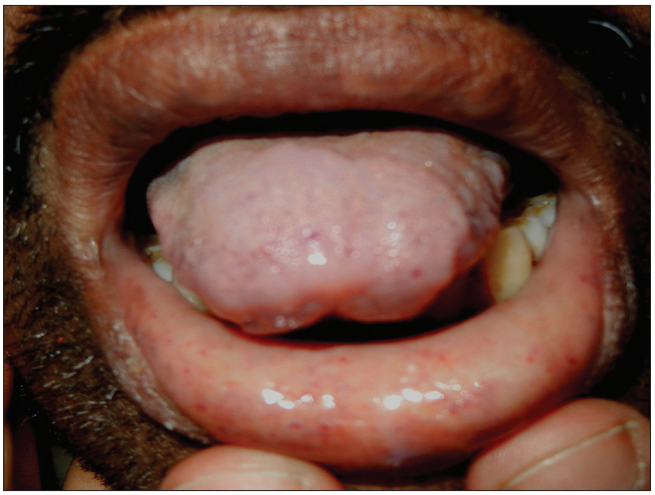

Figure 2: Numerous telangiectatic vessels over lips and tongue

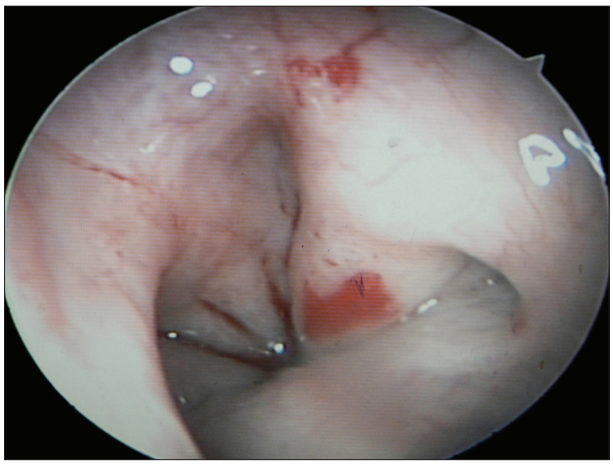

Figure 3: Bleeding spots along with telangiectasia over nasal mucosa

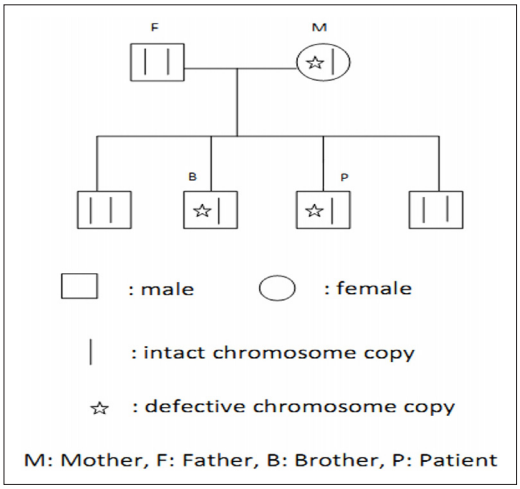

Figure 4: Family tree of first-degree relatives of patient

history should be taken in all patients suspected of having HHT although 20% of cases do not have a family history.[1]

Telangiectasias and arteriovenous malformations in HHT are thought to arise because of changes in angiogenesis, the development of blood vessels out of existing ones. The development of new blood vessels requires the activation and migration of various types of cell, chiefly endothelium, smooth muscle, and pericytes. The exact mechanism by which the HHT mutations influence this process is not yet clear, and it is likely that they disrupt a balance between pro- and antiangiogenic signals in blood vessels. The wall of telangiectasias is unusually friable, which explains the tendency of these lesions to bleed.[7]

Incidence of HHT is difficult to measure because symptoms may vary in severity and epistaxis, commonest presenting symptom of HHT, is often regarded by many as normal. It is believed to affect 1:5000 to 1:10000 populations worldwide.[8] The diagnosis of HHT is currently based on the Curacao Criteria, established by the Scientific Division of the HHT International Foundation which includes (1) spontaneous and recurrent epistaxis; (2) multiple characteristic telangiectasia (lips, tongue, malar prominence and digits); (3) visceral lesions such as pulmonary AVMs, hepatic malformations, G.I telangiectasia with or without bleeding; (4) family history with a first order relative with HHT.[1,9,10] A definitive diagnosis is made if three among the four criteria is present and a probable diagnosis is made if two among the four criteria is present.[1,9,10] Depending on variability of genetic mutation, a number of variants of HHT have been described. Patients with HHT type 1 have higher prevalence of pulmonary and cerebral AVMs and earlier age of presentation whereas hepatic AVMs are most commonly seen in type 2.[11] So our patient probably has type 1 as there was presence of pulmonary AVMs, gastrointestinal bleeding, and absence of hepatic AVMs.

HHT is a genetic disorder by definition. Five genetic types of HHT are recognized. Of these, three have been linked to particular genes, while the two remaining have currently only been associated with a particular locus. More than 80% of all cases of HHT are due to mutations in either endoglin (ENG)- or activin-like receptor kinase 1 (ALK1 or ACVRL1).[12] A total of over 600 different mutations are known. There is likely to be a predominance of either type in particular populations, but the data are conflicting. MADH4 mutations, which cause colonic polyposis in addition to HHT, comprise about 2% of disease-causing mutations. ENG mutations are more likely to cause lung problems while ACVRL1 mutations may cause more liver problems, and pulmonary hypertension may be a particular problem in people with ACVRL1 mutations.[7,12-14]

Genetic tests are available for the ENG, ACVRL1, and MADH4 mutations. Testing is not always needed for diagnosis, because the symptoms are sufficient to distinguish the disease from other diagnoses. There are situations in which testing can be particularly useful. Firstly, children and young adults with a parent with definite HHT may have limited symptoms, if the mutation is known in the affected parent; absence of this mutation in the child would prevent the need for screening tests. Furthermore, genetic testing may confirm the diagnosis in those with limited symptoms who otherwise would have been labeled "possible HHT."[15]

Sequence analysis of the involved genes is the most useful approach (sensitivity 75%), followed by additional testing to detect large deletions and duplications (additional 10%). Not all mutations in these genes have been linked with disease.[15]

Epistaxis being the most common presenting symptom, usually mild and infrequent, does not require any treatment in patients with HHT. However epistaxis resulting in severe anemia is very rare.[16] Pulmonary AVM are more common with HHT type-1 compared with HHT type-2 75% and 44%, respectively.[17] They frequently lead to development of clubbing and polycythemia. The prevalence of intestinal telangiectasia varies between 10% and 33% being most commonly situated in stomach and first part of duodenum.[18] Bleeding is initially mild and increases gradually with age.[16] Up to 70% of patients with HHT may have asymptomatic hepatic involvement in the form of arteriovenous malformations. These may lead to high-output congestive heart failure, portal hypertension and, rarely, liver failure with or without encephalopathy in future.

A number of variants of HHT have been described in the literature. HHT type-1 and type-2 are due to defective ENG and ALK1 genes, respectively. Mutations of ENG are located on the long arm of chromosome 9 (9q33-34), whereas ALK1 mutations are on the long arm of chromosome 12 (12q13). HHT type-3 involves mutations of the long arm of chromosome 5 (5q31.1-32) and type-4 maps to the short arm of chromosome 7 (7p14).[18]

Although iron deficiency anemia has been found in few patients of HHT, it is usually mild and if severe it is found in elderly.[16] But our patient has developed severe anemia at the age of 40 years probably resulting from insensitive gastrointestinal hemorrhage or epistaxis. Our case is also unique in the sense all four criteria mentioned in Curacao's criteria are present in this patient. Although HHT is a very rare disease, its presentation is very classic and a thorough systemic examination is needed to suspect and establish a diagnosis of HHT.

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