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Case report

A challenging case of anemia, respiratory failure and seizures

Carlo Bova[1], Tommaso De Bartolo[2], Roberto De Stefano[3], Martina Ruvio[1]

[1]Department of Internal Medicine [2]Interventional Radiology Unit [3]Pathology Unit, Azienda Ospedaliera, Cosenza, Italy

Abstract. *Background*. Hemorrhagic Hereditary Telangiectasia (HHT), or Rendu-Osler-Weber syndrome, is a rare genetic disorder characterized by mucocutaneous telangiectasias and visceral arteriovenous malformations. *Aim and Methods*.We describe the case of a 64-year old woman in which a multidisciplinary evaluation was useful to interpret an apparently unexplained constellation of symptoms. *Results*. Brain MRI showing ischemic stroke, pulmonary angiography demonstrating arteriovenous malformations, and capsule endoscopy detecting telangiectasias in the jejunum, along with a clinical history of recurrent epistaxis, allowed us to diagnose HHT. *Conclusions.* HHT is rare and difficult to diagnose. A multidisciplinary approach can aid the clinical suspicion. (www.actabiomedica.it)

Key words: Rendu Osler Weber syndrome, Telangiectasia, pulmonary arteriovenous malformation

Introduction

Hemorrhagic Hereditary Telangiectasia (HHT), also known as Rendu-Osler-Weber disease, is a rare disorder due to inherited (autosomal dominant) mutations in either the "ENG"or the "ACVRL1"(more rarely "SMAD4") gene encoding endoglin and ALK1 protein, respectively. As these proteins are responsible for mediating signals in vascular endothelial cells (through beta-transforming growth factor), this leads to a lack of intervening capillaries and direct connections between arteries and veins (1).

Clinical consequences are widespread telangiectasias and vascular malformations, which can cause bleeding, potentially affecting many organs of the body (2). The most common manifestation of the syndrome is epistaxis, but the associated brain and pulmonary lesions are potential sources of relevant morbidity and mortality (3,4). We present the case of a patient with a constellation of apparently unlinked symptoms, in which a multidisciplinary evaluation allowed a proper diagnosis and a partial therapy.

Case Presentation

A 64 year-old white woman was admitted to our hospital because of an episode of seizures and transient left hemiparesis. Her clinical history was significant for repeated episodes of epistaxis and for exertional dyspnea. The clinical examination was remarkable for pale skin and cyanosis of the nails. Small cutaneous telangiectases on the face were at the beginning considered not significant. The oxygen saturation while breating ambient air was 82%. laboratory exams showed severe iron deficiency anemia (hemoglobin level 5.8 g/dl, normal values 12 to 16; serum ferritin level 4 ng/ml, normal range 11 to 307). Fecal occult blood was positive. An echocardiogram and an electroencephalogram were unremarkable. Magnetic resonance imaging (MRI) of the head, performed after the administration of intravenous contrast material, revealed increased signal intensity on diffusion weighted imaging in the cerebellum without associated contrast enhancement, as for ischemic stroke. Low-dose aspirin and Levetiracetam orally were started (but aspirin was

discontinued after the final diagnosis). Gastroduodenoscopy and colonoscopy were normal, while a capsule endoscopy documented multiple telangiectasias in the jejunum, and oral iron supplements were started after a blood trasfusion. To investigate the hypoxia a chest and abdomen computed tomography (CT) with administration of intravenous contrast material was ordered. The exam showed a group of dilated vessels in right upper and lower pulmonary lobes. These lesions were reported as likely arteriovenous malformations (PAVM) (**Figure 1 and 2**).

The CT of the abdomen was unremarkable. The association of recurrent nasal bleeds, cutaneous telangiectasias and visceral vascular malformations allowed us to diagnose HHT (see below). In the attempt to improve the oxygen saturation and to lower the risk of other cerebral adverse events (see below), embolization of the PAVMs was decided. Right heart catheterization was performed and a 8 french catheter was introduced first in the right lower lobar pulmonary artery and then in the upper one. The angiography confirmed the PAVMs and the feeding arteries were embolized through coil occlusion. The procedure led to the exclusion of the PAVMs from the pulmonary circulation (**Figure 3 and 4)**.

Telangiectasias in the jejunum were instead deemed too widespread to be treated. After the embolization the oxygen saturation improved (90% in ambient air) and the patient was discharged with the recommendation to return to the hospital after three months for follow-up.

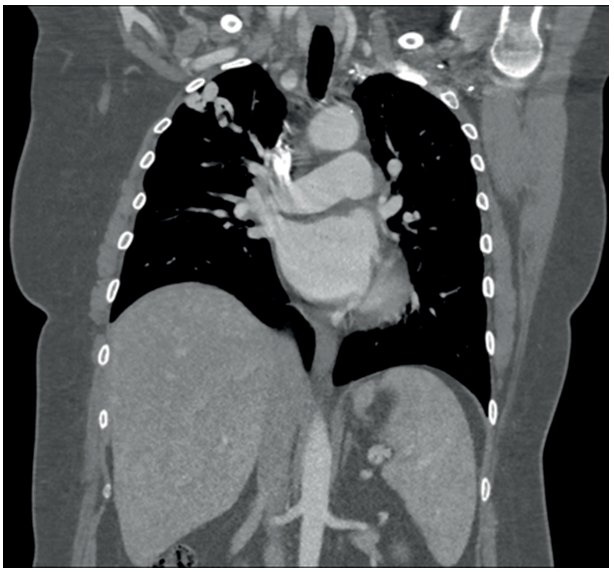

Figure 2. Coronal reformatted image of the chest CT after administration of intravenous contrast material. Dilated vascular structure (arrow) in the right upper lobe.

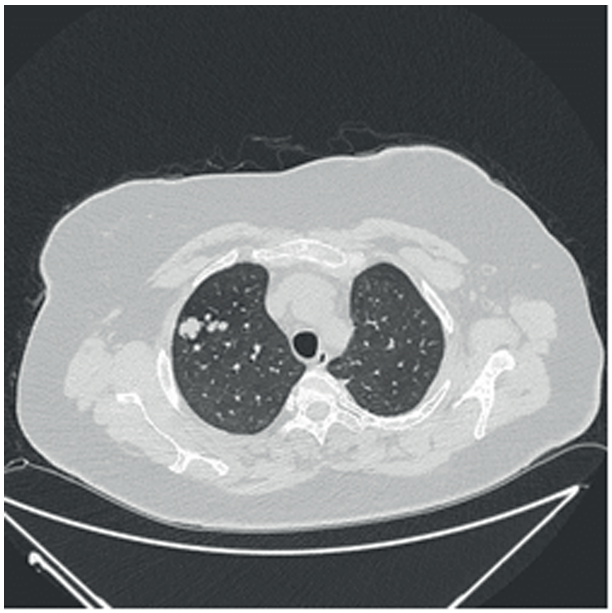

Figure 1. Axial basal chest CT. Serpiginous mass in the right upper lobe (arrow).

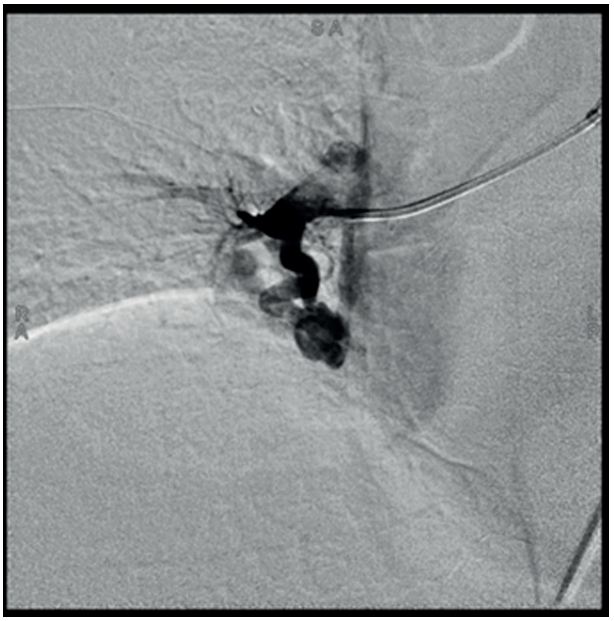

Figure 3. Pulmonary angiography. Arteriovenous malformation of the right upper lobe.

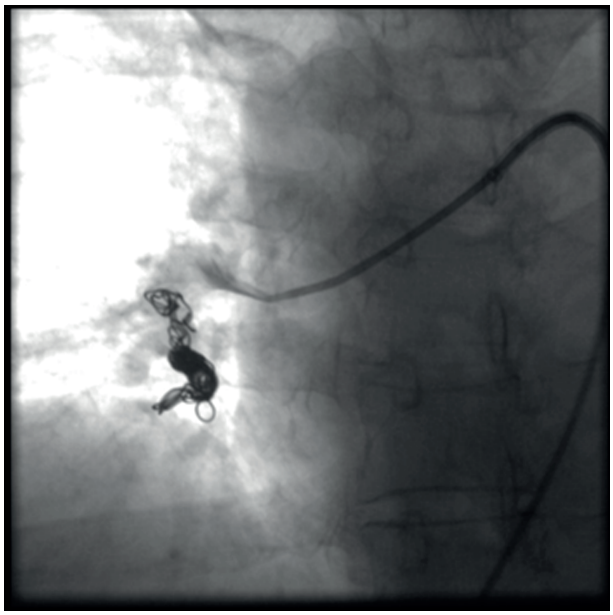

Figure 4. After coil embolization of the feeding artery, the arteriovenous malformation is excluded from the pulmonary circulation.

Discussion

In 1896 Rendu (5) for the first time described a combination of hereditary epistaxis and telangiectases, that subsequently was named Hemorrhagic Hereditary Telangiectasia or Rendu-Osler-Weber disease. This disorder is rare, with a reported prevalence of 10-20 per 100,000 individuals (6). The diagnosis rely on the widely accepted "Curaçao Criteria": telangiectasia on the face, hands and oral cavity; recurrent epistaxis; arteriovenous malformations with visceral involvement; a first degree relative with HHT (7). The diagnosis is considered certain upon the presence of at least 3 of these manifestations, and probable when two of the above criteria are present. Our case met the certainty criteria.

Recurrent epistaxis is the most common manifestation of HHT, affecting about 80% of the patients. Disease severity ranges from massive epistaxis requiring blood transfusions to very mild manifestations. Bleeding starts usually before 21 years of age and become more severe in later decades. Proposed treatments include cauterization, laser ablation, estrogen therapy, septal dermatoplasty, and arterial embolization (2).

Gastrointestinal bleeding is the most common symptom after epistaxis. About 13–30% of HHT patients have blood loss from gastrointestinal tract, usually after 50 years of age (8). Small arteriovenous malformations (telangiectasias) of the gastrointestinal tract are found more frequently in the duodenum (9), and argon plasma coagulation can be used to treat them (9). In our case jejunum lesions were deemed too widespread to be treated.

The liver is involved in about 40-70% of the cases of HHT, but symptomatic involvement is rare (10). Hepatic manifestations include arteriovenous shunts, arterioportal shunts, and portovenous shunts. Congestive heart failure and pulmonary hypertension can occur in large arteriovenous shunts. Arterioportal shunts are rare and associated with portal hypertension. Doppler ultrasound is the first line investigation, while second line techniques are CT or MR. In our case the CT of the abdomen was normal. Embolization of hepatic arteriovenous malformations can result in lethal hepatic infarctions (11), and orthotopic liver transplantation seems to be the only curative option for selected cases (9).

PAVMs are present only in about 5 to 15% of persons with HHT (12), but drive morbidity and mortality (2). They are often multiple and usually appear in both lungs. PAVMs result in direct right-to-left shunts and can lead to dyspnea, fatigue and cyanosis. However, their most serious complications are ischemic strokes or brain abscesses due to paradoxical embolism. Nowadays transcatheter coil occlusion is deemed to be the most appropriate treatment of PAVMs, although recanalization of embolized arteries can occurs (6,13).

Neurological complications affect about 8% to 27% of HHT patients but PAVMs are not the only source of them. In the about a third of the cases, neurologic symptoms are due to cerebral or spinal arteriovenous malformations, that can cause subarachnoid hemorrhage, seizure, or less commonly, paraparesis (2). The treatment of these lesions is not standardized, and include surgical resection, radiosurgery, embolization, and combined modalities (14).

Conclusions

HHT is a rare disorder often with different and apparently unlinked symptoms. This makes the diagnosis difficult. A multidisciplinary approach can help the clinical suspicion.

Authorship: Carlo Bova, Tommaso de Bartolo, Roberto de Stefano, and Martina Ruvio conceived and designed the study. Carlo Bova wrote the manuscript. All the authors contributed to the final version of the manuscript. All authors read and approved the final version of the manuscript.

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Correspondence:
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Carlo Bova,
Department of Internal Medicine, Azienda Ospedaliera,
87100, Cosenza (Italy)
e-mail: carbova@libero.it
ORCID 0000-0002-4162-4202