Case Report

Pulmonary Arterial Hypertension in a Patient With Hereditary Hemorrhagic Telangiectasia

Alejandro Raimondi, a Isabel Blanco, a,∗ Xavier Pomares, b Joan Albert Barbera, c

a Servei de Pneumologia, Hospital Clinic-Institut d’Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Universitat de Barcelona, Barcelona, Spain
b Servei de Pneumologia, Corporació Parc Taulí, Sabadell, Barcelona, Spain
c Centro de Investigaciones Biomédicas en Red de Enfermedades Respiratorias (CIBERES), Spain

ARTICLE INFO

Article history:
Received 17 April 2012
Accepted 20 April 2012
Available online 14 February 2013

Keywords:
Pulmonary hypertension
Arteriovenous malformations
Bosentan
Activin receptor-like kinase 1
Morphogenetic protein receptor II gene
Genetic alterations
Rendu–Osler–Weber syndrome

ABSTRACT

Hereditary hemorrhagic telangiectasia (HHT) is an autosomal dominant disorder characterized by the triad of epistaxis, telangiectasia and vascular malformations. Pulmonary vascular complications associated with this disease include pulmonary arteriovenous malformations (AVM) and, less frequently, pulmonary hypertension (PH).

We report the case of a patient who presented multiple pulmonary AVM and PH probably due to HHT. Embolization was carried out on one of the AVM and the patient received specific pulmonary arterial hypertension treatment with an endothelin receptor antagonist. We also described the patient’s functional and hemodynamic improvement after almost 3 years of follow-up.

© 2012 SEPAR. Published by Elsevier España, S.L. All rights reserved.

Introduction

Hereditary hemorrhagic telangiectasia (HHT), or Rendu–Osler–Weber syndrome, is an autosomal dominant disorder with variable penetrance that is characterized by the presence of epistaxis, telangiectasia and vascular malformations in the pulmonary, gastrointestinal, hepatic and cerebral regions.1 It is a rare disease, with an estimated prevalence of 1:5000 to 1:10000 cases, and has regional variability.2

The presence of vascular pulmonary manifestations is significant. Pulmonary arteriovenous malformations (AVM) can be found in up to 45% of patients with HHT.3 Pulmonary hypertension (PH) is a less frequent complication and can be one of two types: PH associated with hepatic or pulmonary vascular malformations, generally in the context of hyperkinetic states (and frequently associated with episodes of heart failure); and, less frequently, pre-capillary PH as a form of pulmonary arterial hypertension (PAH). Pulmonary hemodynamic studies are the diagnostic tool for differentiating between these two situations.

Palabras clave:
Hipertensión pulmonar
Malformaciones vasculares
Bosentan
Activin receptor-like kinase 1
Gen Bone Morphogenetic protein receptor II
Alteraciones genéticas
Síndrome de Rendu-Osler-Weber

RESUMEN

La hipertensión arterial pulmonar en un paciente con telangiectasia hemorrágica hereditaria (THH) es una enfermedad autosómica dominante caracterizada por la tríada de epistaxis, telangiectasias y malformaciones vasculares. Las complicaciones vasculares pulmonares asociadas a esta enfermedad incluyen malformaciones arteriovenosas (MAV) pulmonares y, de forma menos frecuente, hipertensión pulmonar (HP).

El presente caso clínico hace referencia a un paciente con múltiples MAV pulmonares e HP en el contexto de posible THH. Se procedió a embolización de una MAV y se inició tratamiento específico de hipertensión arterial pulmonar con un antagonista de receptores de endotelina. A continuación se describe su mejoría funcional y hemodinámica tras 3 años de seguimiento.

© 2012 SEPAR. Publicado por Elsevier España, S.L. Todos los derechos reservados.

∗ Corresponding author.
E-mail address: iblanco2@clinic.ub.es (I. Blanco).

1579-2129/5 – see front matter © 2012 SEPAR. Published by Elsevier España, S.L. All rights reserved.
intravascular device, which was done without any complications. Imaging tests showed that the device was correctly inserted (Fig. 1). After the closure of the AVM, the pulmonary hemodynam- 
ics study demonstrated a decrease in CO (3.90 l/min) and transitory in- 
crease of RVP (778 mmHg), which returned to baseline values after 8 h. The pulmonary vascular reactivity test with nitric oxide (NO) inhaled at 40 ppm was not significant. With the diagnosis of 
decapillary PH, treatment was initiated with endothelin receptor antagonist (bosentan at an initial dosage of 62.5 mg/12 h, and after 8 days at 125 mg/12 h).

The patient evolved favorably, showing improved arterial oxygen- 
generation and reduced pulmonary shunt (Qp/Qs).

With the reported family history, and given the fact that HHT is hereditary in nature, a genetic study was done. BMPR2 gene sequencing was normal, and complete sequencing of the ACVR1L (activin A receptor type II-like 1 [ALK1]) gene detected nucleotide variation c.355+ C>T (rs2071218), which has been described in the bibliography as a single nucleotide polymorphism (SNP) with no clinical association with Rendu–Osler–Weber syndrome. However, although the patient is not a carrier of any nucleotide changes that could be considered pathogenic mutations associated 
with the Rendu–Osler–Weber syndrome, not only in the entire codifying region of the ACVR1L gene, but also in the adjacent intronic regions, the absence of mutations in the regions of the ACVR1L gene analyzed cannot confirm or rule out the diagnosis of HHT.

Six months after the closure of the AVM and the start of specific 
P AH treatment, catheterization of the right cavities showed signif- 
cant improvement in pulmonary hemodynamics (Table 1). During the 6-min walk test (6MWT), the patient walked 497 m, which was 
97% of the predicted distance walked without presenting dyspnea or desaturation.

The patient has been followed-up in the pulmonary unit for the last 3 years. He currently presents stable gas exchange (mild hypoxemia, arterial oxygen partial pressure of 68 mmHg and carbon monoxide partial pressure of 35 mmHg, pH 7.43) and func- 
tional class I, without any limitations in exercise capacity.

Discussion

The presence of PH in patients with HHT requires complex studies to determine which type of PH is present (isolated as 
PAH or secondary to hereditary heart syndrome). Our patient present- ed PH, which is clinically and histologically indistinguishable from idiopathic PAH. The pulmonary hemodynamic study showed, in addition to increased PAPm, elevated PVR and PAOP <15 mmHg, ruling out the presence of hyperdynamic and/or hyper- 
kinetic PH.

The current classification of PAH (Dana Point, 2008) includes 
the subgroup of hereditary PAH that encompasses patients with 
idiopathic PAH with germline mutations and cases of family PAH 
with or without identified mutations. The majority of hereditary 
PAH cases are caused by mutations in the bone morphogenetic pro- 	ein receptor type II (BMPR-II), a member of the superfamily of the 
TGF-β receptor. In PAH associated with HHT, no BMPR-II mutations 
were found, although they were found in other genes that code for 
components of the TGF-β receptor, like activin receptor-like kinase 1 (ALK-1) and endoglin (ENG), located in the 12q11-q14 
and 9q34.1 chromosomal regions, respectively. In our patient, we 
detected no BMPR-II mutations, but this does not rule them out 
because we cannot exclude possible mutations in other regions, 
deletions or genetic disorders that were not studied. The single- 
nucleotide polymorphism (SNP) found in the ALK1 gene has not 
been previously associated with HHT or PH.

The simultaneous finding of PAH and pulmonary AVM is uncom- 
mon and merits special attention, since it has been reported that

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Characteristics of the Gas Exchange, Pulmonary Hemodynamics and 6-min Walk Test.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gas exchange</td>
<td>Baseline</td>
</tr>
<tr>
<td>SatO₂, %</td>
<td>82</td>
</tr>
<tr>
<td>PaO₂, mmHg</td>
<td>46</td>
</tr>
<tr>
<td>PaCO₂, mmHg</td>
<td>36</td>
</tr>
<tr>
<td>Qp/Qs, %</td>
<td>28</td>
</tr>
<tr>
<td>Hemodynamics</td>
<td>56/24/35</td>
</tr>
<tr>
<td>CO, l/min</td>
<td>4.53</td>
</tr>
<tr>
<td>HR, l/min/kg</td>
<td>2.62</td>
</tr>
<tr>
<td>PAOP, mmHg</td>
<td>1</td>
</tr>
<tr>
<td>CVP, mmHg</td>
<td>0</td>
</tr>
<tr>
<td>PVR, mmHg</td>
<td>600</td>
</tr>
<tr>
<td>6MWT (FIO₂ 0.21)</td>
<td></td>
</tr>
<tr>
<td>Distance walked, m</td>
<td>260</td>
</tr>
<tr>
<td>% reference value</td>
<td>51</td>
</tr>
<tr>
<td>Initial SatO₂, %</td>
<td>85</td>
</tr>
<tr>
<td>Final SatO₂, %</td>
<td>81</td>
</tr>
</tbody>
</table>

SatO₂, oxygen saturation measured by pulse-oximetry; PaO₂, arterial oxygen partial pressure; PaCO₂, partial pressure of oxygen in mixed venous blood; Qp/Qs, pulmonary short circuit; PAP S/D/M, pulmonary arterial pressure, systolic/diastolic/mean; CO, cardiac output; HR, heart rate; PAOP, pulmonary artery occlusion pressure; CVP, central venous pressure; PVR, pulmonary vascular resistance; 6MWT, 6-min walk test; FIO₂, inspired oxygen fraction.
embolization of AVM can cause an increase in the postload on the right ventricle and trigger acute right cardiac failure.9 There is little evidence about the hemodynamic changes that are expected post-embolization. Shovlin et al.,9 in a study of 143 patients with pulmonary AVM who were embolized, did not document increased pulmonary pressures, although they excluded patients with previous PH. In our case, after embolization we observed a transitory increase in PAPm and PVR, with a slight decrease in CO, without major consequences.

The experience of medical treatment of PAH in HHT is limited to sporadic reports of clinical cases because there are no randomized clinical studies, and given the infrequency of this pathology it is unlikely that they could be developed. Medications approved for the treatment of idiopathic PAH have been used with satisfactory results.10,11 Our patient showed improved functional capacity (as seen in the 6MWT) and pulmonary hemodynamics after treatment was initiated with bosentan.

In conclusion, the hemodynamic characterization of PH in HHT is fundamental for understanding its physiopathology and for determining treatment. Clinical case reports of this rare pathology that evaluate hemodynamic changes, symptoms, functional capacity and response to treatment are useful given the current lack of major scientific evidence.

Conflict of Interests

None of the authors have any conflicts of interest regarding the content of this case report.

References