Founder Mutation C.3344C>T(p.Pro1115Leu) in the EIF2K4 Gene in Iberian Romani Patients With Pulmonary Veno-Occlusive Disease: A Warning for Our Daily Practice

Hallazo de la mutación fundadora C.3344C>T(p.Pro1115Leu) en el gen EIF2K4 en pacientes ibéricos de etnia gitana con enfermedad veno-oclusiva pulmonar: una llamada de atención a nuestra práctica diaria

To the Editor:

Pulmonary veno-occlusive disease (PVOD) is a rare form of pulmonary arterial hypertension. The incidence of this entity is unknown, partly due to underdiagnosis and mistaken classification as idiopathic pulmonary arterial hypertension (IPAH).

PVOD is distinguished by a marked reduction in carbon monoxide diffusing capacity (DLCO) and a typical radiological pattern. It occurs more often in men, and has a more aggressive course than IPAH. Multiple causes, including genetic alterations, have been associated with its development. Recently, homozygous or compound heterozygous mutation of the EIF2K4 gene was described as the cause of PVOD. This mutation appears to occur in 25% of sporadic cases and 100% of familial cases, showing an autosomal recessive inheritance pattern and high penetrance.

Our group has described a homozygous founder mutation C.3344C>T(p.Pro1115Leu) in EIF2K4 in 18 patients from 10 highly consanguineous Romani families with several affected members (Table 1).

All patients developed the disease as young adults (mean: 27.43±7.3 years), and most progressed rapidly to a fatal outcome (death or double-lung transplantation) in the first year after diagnosis.

Although the clinical characteristics of the patients varied on diagnosis, they all had a common trait: severely reduced DLCO.

It is interesting to note that the study of family members revealed a high incidence of death among relatives with no genetic studies but with a history suggestive of PVOD. Moreover, we found an alarming number of family members (59.7%) who were heterozygous carriers of the mutation, generating a risk of new homozygous cases in future generations (Table 1).

At the current time, the Romani population in Spain, a community characterized by a high level of consanguinity, is estimated to be around 750,000 individuals distributed around the whole country. Since this EIF2K4 mutation appears to be typical of the Romani race, and in view of the severity of the disease, we are facing a potentially serious public health problem among this population, which could be partially prevented by early genetic diagnosis and appropriate genetic counseling aimed at reducing the number of new cases.

Therefore, we believe that maintaining a high level of suspicion is essential for Spanish physicians: and that PVOD must be ruled out and a genetic study for EIF2K4 should be performed (as lung biopsy is contraindicated) in those Romani patients presenting with dyspnea and a family history of PAH or severely diminished DLCO. If EIF2K4 homozygous mutations are found, the patient must be rapidly referred to a hospital with an available lung transplantation program being the initiation of pulmonary vasodilators contraindicated due to the high risk of triggering severe pulmonary edema. Moreover, family members of carriers of this mutation must be screened and given appropriate genetic counseling, in order to avoid new cases in future generations and to prevent the propagation of this devastating disease.

Table 1

<table>
<thead>
<tr>
<th>Family</th>
<th>No. of Index Cases</th>
<th>No. of Family Members Studied</th>
<th>No. of Healthy Heterozygous Family Members</th>
<th>No. of Homozygous Family Members Without PVOD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Family 1</td>
<td>3</td>
<td>12</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Family 2</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family 3</td>
<td>4</td>
<td>13</td>
<td>8</td>
<td>1</td>
</tr>
<tr>
<td>Family 4</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Family 5</td>
<td>1</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family 6</td>
<td>3</td>
<td>28</td>
<td>21</td>
<td>1</td>
</tr>
<tr>
<td>Family 7</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Family 8</td>
<td>0</td>
<td>8</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Family 9</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Family 10</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>67</td>
<td>40</td>
<td>2</td>
</tr>
</tbody>
</table>

PVOD: pulmonary veno-occlusive disease.
Funding

Cardiovascular Research Network (RIC) of the Instituto de Salud Carlos III, the Spanish Pulmonary Hypertension Association, Actelion and the Fundación Air Liquide.

References

Paula Navas, a,b,c Jose Julián Rodríguez Reguero, c Pilar Escibano Subías d

a Servicio de Cardiología, Hospital Universitario Gregorio Marañón, Madrid, Spain
b Red de investigación Cardiovascular, Instituto de Salud Carlos III, Madrid, Spain
c Servicio de Cardiología, Hospital Central de Asturias, Oviedo, Asturias, Spain
d Unidad Multidisciplinar de Hipertensión Pulmonar, Servicio de Cardiología, Hospital Universitario Doce de Octubre, Red de investigación Cardiovascular, Instituto de Salud Carlos III, Madrid, Spain

* Corresponding author.
E-mail address: paulanavastejedor@gmail.com (P. Navas).

Hypersensitivity Pneumonitis as a Complication of Intravesical BCG Therapy for Bladder Cancer*

To the Editor,

Hypersensitivity pneumonitis (HP) or extrinsic allergic alveolitis is a pulmonary interstitial disease mainly caused by sensitization to a variety of inhaled organic particles.1 The airborne antigens which most commonly lead to the development of this hypersensitivity reaction are thermophiles, molds, and avian antigens.1 However, some cases caused by non-inhaled medications have also been reported, including exposure to bacillus Calmette-Guérin (BCG) in the treatment of urothelial bladder carcinoma,2 such as the one we describe here.

A 73-year-old man, former smoker (accumulated consumption of 30 pack-years), arterial hypertension, with no known drug allergies. He did not report any occupational or environmental exposure to birds, feathers or other organic substances. He had been diagnosed 3 months previously with superficial papillary urothelial carcinoma and was receiving treatment with intravesical BCG. He was admitted with a 10-day history of acute clinical symptoms, consisting of general malaise, deterioration, and fever 39°C, coinciding with the eighth instillation of BCG. Clinical laboratory results showed leukocytes 11 900 (neutrophils 81%), C-reactive protein 87 mg/dl, and elevated liver function markers (GGT and AP). Tumor markers and angiotensin converting enzyme were normal. Cultures of sputum, urine, bronchoalveolar lavage (BAL), and blood, including Löwenstein-Jensen medium, were negative, as were pneumococcal and Legionella urinary antigen testing. Immunoglobulins (Ig) G and M were normal. Serum IgG (precipitins) for molds, birds, and feathers were negative. Chest HRCT revealed a ground glass pattern in both upper lobes, small centrilobular nodules, and consolidations in the lung bases (Fig. 1(A)). Cell distribution in BAL was: alveolar macrophages 44% and lymphocytes 56%. Flow cytometry immunophenotyping of the lymphocyte

Fig. 1. (A) Chest HRCT. Pulmonary parenchymal window shows a ground glass pattern and small centrilobular nodules in both lung fields. (B) Western blot. Lane 1 shows the serum of an asymptomatic individual receiving BCG; lanes 2, 3, and 4 show the index case after 3, 7, and 51 of corticosteroid therapy. Lane 5 shows the serum of an individual with a history of tuberculosis, and lane 6 is that of a healthy control. The arrow indicates a single band (specific anti-BCG antibodies). (C) Double immunodiffusion of sera 1 and 2. Arrows indicate precipitation bands.

* Please cite this article as: Carasco Hernández L, Castaño Núñez ÁL, Rodríguez Portal JA. Neumonitis por hiperesensibilidad como complicación del tratamiento con BCG intravesical por carcinoma de vejiga. Arch Bronconeumol. 2016;52:445–446.