

has been shown to improve the accuracy of AATD diagnosis.⁹ Most AATD study protocols use isoelectric focusing phenotyping as the gold standard. However, in our case, we decided to use SERPINA1 gene sequencing, due to the limitations of phenotyping in the identification of rare deficiency variants.¹⁰

An interesting finding in our study was the yield obtained from the combination of protein levels and PI*S and Pi*Z allele genotyping (84.9%), which was lower than reported in the literature.⁸ This low yield from the diagnostic protocol is due to the high prevalence of rare deficiency variants, particularly the mutation F76del (PI*Mmalton and PI*Mpalerma) that accounts for 81.5% of the rare variants encountered; this percentage is higher than described in similar studies conducted in Spain.¹¹ Moreover, in the 25 patients who underwent SERPINA1 gene sequencing, we found 20 with NoSnoZ/NoSnoZ, 4 with PI*S/NoSnoZ, and 1 with genotype PI*Z/NoSnoZ with AAT plasma levels discordant with genotyping for the S and Z alleles. Although they were candidates for SERPINA1 full-gene sequencing, this was not performed as the technique was not available in our hospital at the time of the study. We should add that in 3 patients with mild-to-moderate AAT deficiency, no mutations were detected, despite SERPINA1 full-gene sequencing. This may be due to mutations in gene regulatory regions that were not studied,¹² or mutations that are undetectable by sequencing that require alternative techniques for diagnosis.¹³

AATD is one of the most prevalent hereditary diseases in our population, and the mutation F76del, like the PI*Z allele, has been associated with the development of pulmonary emphysema and liver disease,^{14,15} so we believe it is appropriate to detect these mutations in all patients in whom it is impossible to obtain an unequivocal diagnosis with the standard genetic protocols combining serum AAT levels, genotyping for deficiency alleles PI*S and PI*Z, and phenotyping.

References

- Vidal R, Blanco I, Casas F, Jardí R, Miravittles M. Diagnóstico y tratamiento del déficit de alfa-1-antitripsina. Arch Bronconeumol. 2006;42:645–59.
- Stoller JK, Aboussouan LS. A review of α 1-antitrypsin deficiency. Am J Respir Crit Care Med. 2012;185:246–59.
- De Serres FJ, Blanco I, Fernandez-Bustillo E. Genetic epidemiology of alpha-1 antitrypsin deficiency in southern Europe: France, Italy, Portugal and Spain. Clin Genet. 2003;63:490–509.
- Lara B, Blanco I, Martínez MT, Rodríguez E, Bustamante A, Casas F, et al. Spanish registry of patients with alpha-1 antitrypsin deficiency: database evaluation and population analysis. Arch Bronconeumol. 2017;53:13–8.

- García-Palenzuela R, Timiraos Carrasco R, Gómez-Besteiro MI, Lavia G, Lago Pose M, Lara B. Detection of alpha-1 antitrypsin deficiency: a study on patients diagnosed with chronic obstructive pulmonary disease in primary health care. Emergen. 2016. <http://dx.doi.org/10.1016/j.semerg.2016.05.003>.
- Morris H, Morgan MD, Wood AM, Smith SW, Ekeowa UI, Herrmann K, et al. ANCA-associated vasculitis is linked to carriage of the Z allele of α 1-antitrypsin and its polymers. Ann Rheum Dis. 2011;70:1851–6.
- Moral P, Esteban E, Vives S, Valveny N, Toja DI, Gonzalez-Reimers E. Genetic study of the population of Tenerife (Canary Islands, Spain): protein markers and review of classical polymorphisms. Am J Phys Anthropol. 1997;102:337–49.
- Snyder MR, Katzmann JA, Butz ML, Wiley C, Yang P, Dawson DB, et al. Diagnosis of alpha-1-antitrypsin deficiency: an algorithm of quantification, genotyping, and phenotyping. Clin Chem. 2006;52:2236–42.
- Graham RP, Dina MA, Howe SC, Butz ML, Willkomm KS, Murray DL, et al. SERPINA1 full-gene sequencing identifies rare mutations not detected in targeted mutation analysis. J Mol Diagn. 2015;17:689–94.
- Sub-Lailam BB, Procter M, Krautscheid P, Haas J, Kumar S, Mao R, et al. Challenging identification of a novel PiSf and the rare PiMmaltonZ 1-antitrypsin deficiency variants in two patients. Am J Clin Pathol. 2014;141:742–6.
- Rodríguez-Frias F, Miravittles M, Vidal R, Camos S, Jardí R. Rare alpha-1-antitrypsin variants: are they really so rare? Ther Adv Respir Dis. 2012;6:79–85.
- Chappell S, Daly L, Morgan K, Guetta Baranes T, Roca J, Rabinovich R, et al. Cryptic haplotypes of SERPINA1 confer susceptibility to chronic obstructive pulmonary disease. Hum Mutat. 2006;27:103–9.
- Takahashi H, Crystal RG. Alpha 1-antitrypsin Null(isola di procida): an alpha 1-antitrypsin deficiency allele caused by deletion of all alpha 1-antitrypsin coding exons. Am J Hum Genet. 1990;47:403–13.
- Joly P, Guillaud O, Hervieu V, Francina A, Mornex JF, Chapuis-Cellier C. Clinical heterogeneity and potential high pathogenicity of the Mmalton Alpha 1 antitrypsin allele at the homozygous, compound heterozygous and heterozygous states. Orphanet J Rare Dis. 2015;10:130.
- Figueira Gonçalves JM, Martínez Bugallo F, Díaz Pérez D, Martín Martínez MD, García-Talavera I. Déficit de alfa-1-antitripsina asociado a la variante Mmalton. Descripción de una familia. Arch Bronconeumol. 2016;52:617–8.

Francisco Martínez Bugallo,^{a,*} Juan Marco Figueira Gonçalves,^b María Dolores Martín Martínez,^a David Díaz Pérez^b

^a Unidad de Diagnóstico Molecular, Servicio de Análisis Clínicos, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain

^b Servicio de Neumología, Hospital Universitario Nuestra Señora de Candelaria, Santa Cruz de Tenerife, Spain

* Corresponding author.

E-mail address: fmarbug@gobiernodecanarias.org (F. Martínez Bugallo).

1579-2129/

© 2017 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.

Reversible Interferon-Induced Pulmonary Arterial Hypertension in a Patient With Multiple Sclerosis^{*}



Hipertensión arterial pulmonar reversible en una paciente con esclerosis múltiple asociada a tratamiento con interferón

To the Editor,

Interferon (IFN) is a drug with antiviral, antibacterial, and anti-tumor activity, which is used in the treatment of chronic hepatitis C virus infection (IFN- α) and multiple sclerosis (IFN- β) and is currently considered a possible risk factor for pulmonary arterial

hypertension (PAH).^{1,2} This association is based on the observation of isolated cases of PAH potentially associated with exposure to IFN- α or IFN- β ,^{3,4} some of which were reversible after discontinuing the drug.^{5,6}

We report the case of a 31-year-old woman with no clinical history of interest, diagnosed with multiple sclerosis in 2010, and receiving subcutaneous IFN- β since then.

She was hospitalized in May 2016 due to dyspnea on exertion and central chest pain; a few hours after admission, she had an episode of syncope and hypotension, and was transferred to the intensive care unit where an echocardiogram was performed, which revealed severe pulmonary hypertension probably due to tricuspid regurgitation and right ventricular dilation. CT-angiography was performed and no pulmonary embolism was found.

Given these findings, treatment began with sildenafil and anticoagulation. Despite treatment, her progress was poor, and she was referred to our unit for evaluation.

^{*} Please cite this article as: García Ortega A, López Reyes R, Torrents Vilar A, Zaldivar Olmeda E, Prado Barragan M. Hipertensión arterial pulmonar reversible en una paciente con esclerosis múltiple asociada a tratamiento con interferón. Arch Bronconeumol. 2017;53:596–597.

The initial physical examination showed blood pressure 114/90 mmHg without the need for vasoactive drugs, heart rate 110 bpm, SpO₂ 97% on 1 lpm oxygen, increased intensity of pulmonary second sound (P₂), and presence of congestive signs.

The diagnosis was PAH with severe right ventricular involvement and secondary cardiorespiratory failure, and an investigation of the etiology began in line with European guidelines. Complete blood count and biochemistry results were normal, serology for hepatotropic viruses and HIV were negative, and autoimmunity was normal. Elevated pro-BNP values were observed (2680 pg/ml). Electrocardiogram showed sinus rhythm with evidence of right overload. Respiratory disease was ruled out by lung function tests and CT. DLCOc was 56.3 ml/min/mmHg. A 6-minute walk test (6MWT) was performed, in which the patient walked 450 m with an end saturation of 88%. Doppler ultrasound and V/Q scintigraphy were normal. The echocardiogram showed severe ventricular dilation with significant systolic dysfunction (TAPSE 12 mm and FAC 30%), free wall hypertrophy (7.5 mm), dilated right atrium and moderate tricuspid failure, with a 60 mmHg gradient, giving an estimated PaSp of 75 mmHg, mild pericardial effusion, dilated inferior vena cava, with no inspiratory collapse; left cavities were normal. Right heart catheterization (RHC) identified PAH: mPAP 59 mmHg, PCP 13 mmHg, CO 4.6 l/m, 60% SvO₂, DBP 17 mmHg, RVP 10 WU, and negative vasoreactivity test.

In view of the patient's history and the results of the additional examinations, the administration of IFN was considered the most likely cause of the PAH. The patient was diagnosed as having severe PAH with an intermediate-high risk profile, so IFN- β was discontinued, and ambrisentan and inhaled iloprost were added to her initial treatment.

The patient was discharged 15 days after admission in a stable clinical condition with significant functional improvement. After 6 months of follow-up, her functional class was I/IV, pro-BNP had normalized (56 pg/ml), follow-up 6MWT, at 555 m without desaturation, had improved, and echocardiography showed significant improvement, with normalization of right heart morphology and function. A follow-up RHC in December 2016 showed mPAP 32 mmHg, PCP 12 mmHg, CO 7.8 l/m, DBP 5 mmHg and RVP 3.2 UW.

PAH associated with IFN treatment is a rare entity with few published cases, and should be considered in all patients receiving IFN who develop dyspnea with no other identifiable cause. The first case was published in 1993, although the diagnosis of PAH was made without hemodynamic confirmation.⁷ More recently, the French group has published a retrospective analysis of 53 cases of PAH with history of exposure to IFN,⁸ 48 receiving IFN- α for chronic hepatitis C and 5 receiving IFN- β for multiple sclerosis. Most patients in the first group had another risk factor associated with PAH (85% portal hypertension and 56% HIV), and in the second group, 1 patient had an atrial septal defect. In most cases the diagnosis was made within 3 years after starting treatment with IFN.⁸

Sixteen patients continued treatment with IFN after the diagnosis of PAH was established. This treatment was associated with a functional and hemodynamic decline that required additional PAH treatment, suggesting that IFN could act as a factor triggering the development of PAH, even in the presence of other known or undiagnosed predisposing factors.⁸

According to current evidence, IFN- β -induced PAH is less common and differs in some aspects: 13 cases have been published

since 2009,⁹ most of which lacked risk factors for PAH, all were women, and the period between exposure and the onset of symptoms was greater (1–15 years). PAH was severe in all cases, and most required combined treatment.^{5,8,9}

Our patient had no other known concomitant factors, and while it is true that, according to her sex and age, her PAH may have been idiopathic, our suspicion that it was caused by IFN is based on the following: 1) the cause-and-effect relationship with the development of pulmonary vascular disease after 5 years of IFN exposure; 2) the significant improvement after discontinuing IFN, that can hardly be explained by the use of specific vasodilator treatment.

In spite of cases like ours and the data available from basic research studies suggesting that the IFN may be involved in the development of PAH, the role of IFN in PAH is still unclear, so it must be considered as a possible risk factor.^{1,2} Prospective case-control studies will be necessary to definitively establish the relationship between IFN exposure and PAH, and experimental research is needed for the in-depth study of the underlying physiopathological mechanism.

References

- Galiè N, Humbert M, Vachiery JL, Gibbs S, Lang I, Torbicki A, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: the Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for the European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Respir J*. 2015;46:903–75.
- Montani D, Seferian A, Savale L, Simonneau G, Humbert M. Drug-induced pulmonary arterial hypertension: a recent outbreak. *Eur Respir Rev*. 2013;22:244–50.
- George PM, Oliver E, Dorfmueller P, Dubois OD, Reed DM, Kirkby NS, et al. Evidence for the involvement of type I interferon in pulmonary arterial hypertension. *Circ Res*. 2014;114:677–88.
- Anderson RD, Thompson A, Burns AT. Pulmonary arterial hypertension associated with the use of interferon therapy for chronic hepatitis C infection complicated by extrinsic left main coronary artery compression. *Intern Med J*. 2014;44:1027–30.
- Savale L, Chaumais MC, O'Connell C, Humbert M, Sitbon O. Interferon-induced pulmonary hypertension: an update. *Curr Opin Pulm Med*. 2016;22:415–20.
- Caravita S, Secchi MB, Wu SC, Pierini S, Paggi A. Sildenafil therapy for interferon-beta-1a-induced pulmonary arterial hypertension: a case report. *Cardiology*. 2011;120:187–9.
- Kramers C, de Mulder PH, Barth JD, Wagener DJ. Acute right ventricular heart failure in a patient with renal cell carcinoma after interferon therapy. *Neth J Med*. 1993;42:65–8.
- Savale L, Sattler C, Gunther S, Montani D, Chaumais MC, Perrin S, et al. Pulmonary arterial hypertension in patients treated with interferon. *Eur Respir J*. 2014;44:1627–34.
- Ledinek AH, Jazbec SS, Drinovec I, Rot U. Pulmonary arterial hypertension associated with interferon beta treatment for multiple sclerosis: a case report. *Mult Scler*. 2009;15:885–6.

Alberto García Ortega, Raquel López Reyes,* Ana Torrents Vilar, Enrique Zaldivar Olmeda, Marcos Prado Barragan

Servicio de Neumología, Hospital Universitari i Politènic La Fe, Valencia, Spain

* Corresponding author.

E-mail address: raquel.lopez@separ.es (R. López Reyes).

1579-2129/

© 2017 SEPAR. Published by Elsevier España, S.L.U. All rights reserved.