Rev Esp Cardiol. 2023;76(12):954–955

Editorial

Chronic Whipple's disease, a diagnostic challenge for the cardiologist

La enfermedad de Whipple crónica, un reto diagnóstico para el cardiólogo

Pilar Escribano Subías[a,b,*]

[a] Unidad de Hipertensión Pulmonar, Servicio de Cardiología, Hospital Universitario 12 de Octubre, Madrid, Spain
[b] Centro de Investigación Biomédica en Red de Enfermedades Cardiovasculares (CIBERCV), Spain

Article history:
Available online 19 October 2023

Whipple disease is a multisystemic disorder caused by *Tropheryma whipplei*, a gram-positive bacillus first cultured in the year 2000. The disease has a prodromal stage that precedes the classic systemic or gastrointestinal stage by an average of 6 years. *T. whipplei* infection occurs via the gastrointestinal route, causing extensive recruitment of macrophages with subsequent absorption of bacteria and production of proinflammatory cytokines such as interleukin (IL) 1b and IL-16. The inability to degrade bacterial antigens due to decreased IL-12 production and apoptosis of recruited macrophages triggers further bacterial spread and multiorgan involvement.[1]

The prodromal stage is marked by nonspecific symptoms, mainly in the form of arthralgia and arthritis. The hallmark features of the classic or chronic form of Whipple disease are gastrointestinal disease with weight loss, abdominal pain, diarrhea, and arthralgia in up to 80% of affected individuals, together with fever and multiple enlarged mediastinal, mesenteric, and retroperitoneal lymph nodes. Little has been published on cardiac manifestations, but the most common finding is bacterial endocarditis with negative blood cultures; myocarditis and pericarditis are less common.[2] Pulmonary hypertension (PH) associated with Whipple disease is extremely rare, with just a few reports in the literature.[3,4]

In this issue of *Revista Española de Cardiología*, Gallo Fernández et al.[5] present a case of PH associated with Whipple disease selected from the 2023 League of Clinical Cases of the Spanish Society of Cardiology (SEC).[6] In this article, discuss the diagnosis step by step.

At the onset of symptoms, the patient, a woman, presented to the emergency room with manifestations of heart failure (HF) and systemic and pulmonary congestive symptoms, evident in the physical examination and chest radiograph findings. She was initially treated with diuretics. Computed tomography ruled out pulmonary embolism. Ultrasound examination showed dilation of the right cavities, leading to a tentative diagnosis of idiopathic primary PH.

It is important to note at this point that pulmonary embolism does not lead to left HF with crackles or signs of pulmonary congestion on chest radiography. At the same time, clear signs of pulmonary congestion rule out PH.

PH is characterized by remodeling of the pulmonary arterioles with a loss of pulmonary vascular bed functioning and a progressive increase in pulmonary vascular resistance (PVR), which leads to right HF without pulmonary congestion. The process is gradual, and the severity of the hemodynamic profile of PH is proportional to the ensuing signs and symptoms of right HF. Patients with PH and HF with systemic congestion requiring treatment with high-dose diuretics have altered hemodynamic values, characterized by reduced cardiac output and cardiac index, increased right atrial pressure, increased mean pulmonary artery pressure (mPAP) ($\geq$ 35 mmHg), and PVR $>$ 5 Wood units (WU). The mPAP in our patient was 25 mmHg and the remaining hemodynamic variables were described as normal. In general terms, a patient with slightly increased mPAP (25 mmHg) and normal cardiac output would be paucisymptomatic and only experience dyspnea during intense exertion. Mild PH would not cause severe HF. Of note, pulmonary capillary wedge pressure (PCWP) during right heart catheterization was normal after treatment with diuretics. The PCWP must have been high at admission, and probably explains the crackles detected on auscultation and the pulmonary congestion observed on the chest radiograph. In other words, the patient had group 2 PH (mediated by elevated left ventricular filling pressures and not by a primary vascular disease of the pulmonary vascular bed).

Nonetheless, a primary condition involving the pulmonary vessels could not be ruled out. Autopsy studies of patients who died of Whipple disease have described small clumps of bacilli and isolated organisms within the tunica media, as well as small areas of focal degeneration of the tunic media surrounding the areas invaded by the bacilli and intimal proliferation of the affected pulmonary vessel.[7] Macrophages containing bacilli were also observed in the adventitia of the pulmonary arteries. Considering the pathobiology of *T. whipplei* infection, a proinflammatory environment within the pulmonary vasculature mediated by proinflammatory cytokines (transforming growth factor β) could also lead to PH. Accordingly, in the context of multisystemic *T. whipplei* infection, direct injury to the pulmonary vessels may have contributed to the development of PH.

Two months later, the patient was readmitted with evident multisystem complications and no signs of worsening HF, which was successfully controlled with high-dose diuretics. Asthenia, anorexia, and major weight loss are classic signs of Whipple disease, as are enlarged mesenteric and retroperitoneal lymph

SEE RELATED CONTENT:
https://doi.org/10.1016/j.rec.2023.06.004

* Corresponding author.
E-mail address: pilar.escribano.subias@gmail.com

https://doi.org/10.1016/j.rec.2023.06.018

nodes. Positron emission tomography-computed tomography showed extensive intestinal inflammation, and the diagnosis of Whipple disease was confirmed by stool polymerase chain reaction and an intestinal biopsy. Further testing revealed tricuspid endocarditis. Endocarditis is the most common heart condition in patients with Whipple disease and tends to progress favorably with long-term antithrombotic treatment.

The case reported by Gallo Fernández et al.[5] illustrates the difficulty of diagnosing Whipple disease in Spain. Not only is it uncommon in this setting, but it also has a wide variety of clinical presentations. Mild PH detected during right heart catheterization does not support a diagnosis of severe HF. The literature, however, contains reports of HF requiring inotropic support and intensive care admission in patients with severe PH (PVR $>$ 6 WU). PH secondary to Whipple disease responds poorly to pulmonary vasodilators, which are essentially used as support therapy until antibiotics bring the infection under control. Once this occurs, the PH resolves and does not require long-term pulmonary vasodilator treatment. HF follows a similar clinical course.

FUNDING

None.

CONFLICTS OF INTEREST

None.

REFERENCES

1. Pankl S, Báez M, Young P, et al. Enfermedad de Whipple e hipertensión pulmonar reversible. *Medicina (B Aires).* 2021;81:91–95.
2. Lagier JC, Share RD. Whipple's disease and Tropheryma whipplei infections: when to suspect them and how to diagnose and treat them. *Curr Opin Infect Dis.* 2018;31:463–470.
3. Camboulive A, Jutant E-M, Savale L, et al. Reversible pulmonary hypertension associated with multivisceral Whipple's disease. *Eur Respir J.* 2021;57:2003132.
4. Baloira A, Núñez M, Tumbeiro M, Parente-Lamelas I, Bastos M, Gutiérrez M. Pulmonary hypertension associated with Whipple disease. *Eur Respir Rev.* 2014;23:533–536.
5. Gallo Fernández I, Rodríguez Nieto J, Perea Armijo J, Pastor Wulf D, López Baizán J, Delgado Ortega M. Mujer de mediana edad con síntomas congestivos, algo más que hipertensión arterial pulmonar. *Rev Esp Cardiol.* 2023. http://dx.doi.org/10.1016/j.recesp.2023.04.010.
6. Sociedad Española de Cardiología. Liga de los Casos Clínicos. 2023. Available from: https://ligacasosclinicos.com/. Accessed 20 may. 2023.
7. James TN, Bulkley BH. Whipple bacilli within the tunica media of pulmonary arteries. *Chest.* 1984;86:454–458.