EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Research letter

Reversible pulmonary hypertension associated with multivisceral Whipple's disease

Alice Camboulive, Etienne-Marie Jutant, Laurent Savale, Xavier Jaïs, Olivier Sitbon, Charlotte Mussini, Jérémie Bénichou, Jean-Christophe Lagier, Marc Humbert, David Montani

Please cite this article as: Camboulive A, Jutant E-M, Savale L, *et al*. Reversible pulmonary hypertension associated with multivisceral Whipple's disease. *Eur Respir J* 2020; in press (https://doi.org/10.1183/13993003.03132-2020).

Reversible pulmonary hypertension associated with multivisceral Whipple's disease

Alice Camboulive[1,2,3]*, Etienne-Marie Jutant, MD[1,2,3]*, Laurent Savale, MD, PhD[1,2,3], Xavier Jaïs[1,2,3], Olivier Sitbon, MD, PhD[1,2,3], Charlotte Mussini[4], Jérémie Bénichou[5], Jean-Christophe Lagier[6], Marc Humbert MD, PhD[1,2,3], David Montani, MD, PhD[1,2,3]

* Contributed equally

[1] Assistance Publique - Hôpitaux de Paris (AP-HP), Department of Respiratory and Intensive Care Medicine, Pulmonary Hypertension National Referral Center, Hôpital Bicêtre, Le Kremlin-Bicêtre, France

[2] Université Paris-Saclay, School of Medicine, Le Kremlin-Bicêtre, France

[3] INSERM UMR_S 999 "Pulmonary Hypertension: Pathophysiology and Novel Therapies", Hôpital Marie Lannelongue, Le Plessis-Robinson, France

[4] AP-HP, Service d'Anatomie et de Cytologie Pathologiques, Hôpital de Bicêtre, 94270 Le Kremlin Bicêtre, France, Hôpitaux Universitaires Paris-Saclay, Le Kremlin-Bicêtre, France

[5] AP-HP, Service d'ophtalmologie, Hôpital de Bicêtre, 94270 Le Kremlin Bicêtre, France, Hôpitaux Universitaires Paris-Saclay, Le Kremlin-Bicêtre, France

[6] Aix Marseille University, IRD, AP-HM, MEPHI, 13005 Marseille, France; IHU-Méditerranée Infection, 13005 Marseille, France

Correspondence:
David Montani, MD, PhD
Service de Pneumologie, Hôpital Bicêtre
78, Rue du général Leclerc, 94270 Le Kremlin-Bicêtre, France.
Tel: +331 45217976; Fax: +331 45217971
mailto: david.montani@aphp.fr

Take-home message: We report a case of multivisceral Whipple's disease with severe precapillary pulmonary hypertension cured by doxycycline and hydroxychloroquine therapy associated with initial oral combination of bosentan and tadalafil.

Key-words: Whipple's disease, Pulmonary hypertension

Word count: 1159

Figures: 1

Whipple's disease (WD) is a rare infectious disease developed through fecal-oral transmission and caused by *Tropheryma whipplei*, a ubiquitous gram bacillus [1]. The pathogenesis remains unclear, and several host factors seem to be implicated, including male sex, comorbidities and genetic susceptibility [1]. WD is a multivisceral disorder with frequent gastro-intestinal, joint and neurological involvement, as well as pulmonary, cardiovascular, mucocutaneous, and ophthalmologic lesions [2]. The diagnosis is made via small bowel biopsy with Periodic Acid Schiff staining (PAS) positivity and by polymerase chain reaction (PCR) on different biological samples [1]. Classical treatment requires prolonged antibiotic therapy and allows rapid improvement. The association of doxycycline and hydroxychloroquine over one year followed by lifetime treatment with doxycycline has been shown to lead to good clinical responses and fewer relapses [3]. Others have recommended initial use of intravenous antibiotics, followed by trimethoprim-sulfamethoxazole for one year [4]. Among lung complications of WD, pulmonary hypertension (PH) is very rare and remains poorly understood [5–8]. Here, we report the first well-documented case of a man with concomitant diagnosis of severe precapillary PH and multivisceral WD who had total reversibility in hemodynamics and clinical state after treatment of WD and PH.

A 54-year-old Caucasian man, a technician for phonelines and former smoker (18 pack-years), with a medical history of gastro-esophageal reflux and systemic hypertension treated by beta-blockers, was hospitalized for acute right heart failure in the respiratory intensive care unit. He reported a deterioration in general state over the previous year with fatigue, a weight loss of 15 kilograms, diarrhea, a change in mood and episodes of acute left red eye with spontaneous resolution. In April 2019, he presented to the emergency department with progressive dyspnea that had been worsening for a few weeks. Clinical examination showed signs of right heart failure, biology showed a microcytic anemia and increased N-terminal pro-B-type natriuretic

peptide and transthoracic echocardiography showed dilation of the right heart chambers, increased estimated systolic pulmonary artery pressure (sPAP 65 mmHg) and right ventricular dysfunction (tricuspid annular plane systolic excursion TAPSE 12 mm). Computed tomography pulmonary angiography revealed right heart dilation, with no evidence of acute pulmonary embolism and normal lung parenchyma (**Figure 1**). He had no family history or exposures to drugs and toxins. Right heart catheterization (RHC) confirmed severe precapillary PH without acute pulmonary vasodilator response to inhaled nitric oxide: mean PAP (mPAP) 40 mmHg, cardiac output 3,1 L/min, cardiac index 2 L/min/m^2, pulmonary artery wedge pressure (PAWP) 13 mmHg, and pulmonary vascular resistance (PVR) 8 WU. Treatment with intravenous dobutamine and diuretics was initiated together with oral dual combination of PAH drugs (bosentan and tadalafil). Evolution was favorable, and dobutamine was stopped after 5 days. Clinical investigations found no evidence for other conditions associated with group 1 PAH (such as connective tissue disease, congenital heart disease, portal hypertension, or HIV infection), group 3 PH due to chronic respiratory diseases, or group 4 chronic thromboembolic PH (normal ventilation perfusion scan). Because of the associated weight loss, diarrhea and microcytic anemia, a gastroscopy was performed, and duodenal biopsies showed infiltration of the lamina propria by foamy PAS-positive macrophages (**Figure 1**). As gastroscopy could be at high risk in patients with PH, it was performed in the intensive care unit with a mild sedation and careful medical supervision. *T. whipplei* PCR was positive in the saliva but negative in the cerebrospinal fluid. He also presented a congestive left eye with ptosis, exophthalmia, conjunctival injection, moderate visual loss and periorbital inflammation with limited eye movements and increased intraocular pressure **(Figure 1)**. Orbital magnetic resonance imaging confirmed left exophthalmia and inflammatory pseudo-tumor of the left orbit **(Figure 1).** Doxycycline (100 mg x 2 per day) and hydroxychloroquine (200 mg x 3 per day) were started. After 2 months, the patient's evolution was remarkable: he experienced great improvements in his general state (+ 13

kilograms in 9 months), with total correction of all initial symptoms. Repeated hemodynamic measurements (at 5, 9 and 14 months) showed a complete correction of PH (mPAP < 20 mmHg, PVR < 3 WU), and bosentan and tadalafil were sequentially stopped without recurrence of PH. Fourteen months after diagnosis and five months after interruption of PAH therapy, he had no exercise limitations in New York Association functional class I, with 610 m 6-minute walk distance and a peak VO_2 at 85% of the theoretical maximum (26.4 mL/kg/min), with normal biological markers, including NT pro-BNP (141 mg/mL). C-reactive protein (CRP) which was 107 mg/L at the diagnosis remained < 5 mg/L during the follow-up. He continued on combined doxycycline and hydroxychloroquine for one year and will continue doxycycline for life to prevent WD relapses. He had no side effects from the treatments, and repeated electrocardiograms showed no QT interval prolongation with hydroxychloroquine.

In the literature, we found 10 case reports of PH associated with WD, not always confirmed by RHC [5–7]. Six cases were well documented with evidence of precapillary PH [7]. Among these 10 patients, 80% had favorable evolution with antibiotic therapy (intravenous beta-lactam antibiotics followed by trimethoprim-sulfamethoxazole in six cases and doxycycline associated with hydroxychloroquine in the remaining two) [6–8]. Three patients were prescribed calcium channel blockers (associated with phosphodiesterase type 5 inhibitor in one), but this therapy failed with worsening of symptoms, even in the case with acute response to vasodilators [7]. One patient died after a valve replacement for aortic insufficiency [7]. The hemodynamic evolution after treatment was well documented by RHC in only two patients [7].

Our patient is the first reported case with favorable outcomes of WD and PH after treatment with doxycycline and hydroxychloroquine associated with initial oral combination of bosentan and tadalafil [9]. The pathophysiology of precapillary PH in WD remains unclear. Pulmonary artery

infiltration by T. whipplei in the tunica media has been suspected, along with small pulmonary artery obliteration by macrophages and fibrinoid debris [10]. Our present case of excellent clinical and hemodynamic outcomes with WD therapy argue in favor of reversible pulmonary vascular involvement. One hypothesis for this reversible vascular involvement may be an excessive inflammation and dysregulated immunity response in the pulmonary vascular wall, as observed in systemic arteries with signs of arteritis [11] and in intestinal cells, with down-regulation of MHC class II promoting local accumulation of bacteria and inflammation [12] and consistent with the decrease in CRP during the follow-up in our patient.

In conclusion, we report a case of multivisceral WD with severe precapillary PH cured by doxycycline and hydroxychloroquine therapy associated with initial oral combination of bosentan and tadalafil. PH did not relapse after weaning from bosentan and tadalafil. Based on this remarkable evolution, also observed in other case reports, the causal link between WD and PH appears strong, even if data are currently insufficient to provide a thorough understanding of the mechanisms leading to PH in that setting [13]. Based on this case and a literature review, we propose to classify PH associated with WD within group 5 PH with unclear and/or multifactorial mechanisms [14].

REFERENCES

1. Marth T, Moos V, Müller C, Biagi F, Schneider T. Tropheryma whipplei infection and Whipple's disease. *Lancet Infect Dis* 2016; 16: e13-22.

2. Lagier J-C, Lepidi H, Raoult D, Fenollar F. Systemic Tropheryma whipplei: Clinical Presentation of 142 Patients With Infections Diagnosed or Confirmed in a Reference Center. *Medicine* 2010; 89: 337–345.

3. Lagier J-C, Fenollar F, Lepidi H, Giorgi R, Million M, Raoult D. Treatment of classic Whipple's disease: from in vitro results to clinical outcome. *J. Antimicrob. Chemother.* 2014; 69: 219–227.

4. Feurle GE, Junga NS, Marth T. Efficacy of ceftriaxone or meropenem as initial therapies in Whipple's disease. *Gastroenterology* 2010; 138: 478–486; quiz 11–12.

5. Riemer H, Hainz R, Stain C, Dekan G, Feldner-Busztin M, Schenk P, Müller C, Sertl K, Burghuber OC. Severe pulmonary hypertension reversed by antibiotics in a patient with Whipple's disease. *Thorax* 1997; 52: 1014–1015.

6. Brevet P, Rottenberg P, Viacroze C, Schleifer D, Lequerre T, Vittecoq O. A case of Whipple's disease mimicking auto-inflammatory disease and revealed by severe right cardiac failure under anakinra. *Joint Bone Spine* 2020; 87: 365–366.

7. 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.

8. Lochouarn M, Lagier J-C, Raoult D, Pulcini C. A case of Whipple's disease evolving over 30 years. *Med Mal Infect* 2014; 44: 331–333.

9. Galiè N, Channick RN, Frantz RP, Grünig E, Jing ZC, Moiseeva O, Preston IR, Pulido T, Safdar Z, Tamura Y, McLaughlin VV. Risk stratification and medical therapy of pulmonary arterial hypertension. *Eur. Respir. J.* 2019; 53.

10. James TN, Bulkley BH. Whipple bacilli within the tunica media of pulmonary arteries. *Chest* 1984; 86: 454–458.

11. James TN, Haubrich WS. De subitaneis mortibus. XIV. Bacterial arteritis in Whipple's disease. *Circulation* 1975; 52: 722–731.

12. Ectors NL, Geboes KJ, De Vos RM, Heidbuchel HP, Rutgeerts PJ, Desmet VJ, Vantrappen GR. Whipple's disease: a histological, immunocytochemical, and electron microscopic study of the small intestinal epithelium. *J. Pathol.* 1994; 172: 73–79.

13. Humbert M, Guignabert C, Bonnet S, Dorfmüller P, Klinger JR, Nicolls MR, Olschewski AJ, Pullamsetti SS, Schermuly RT, Stenmark KR, Rabinovitch M. Pathology and pathobiology of pulmonary hypertension: state of the art and research perspectives. *Eur. Respir. J.* 2019; 53.

14. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Souza R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur. Respir. J.* 2019; 53.

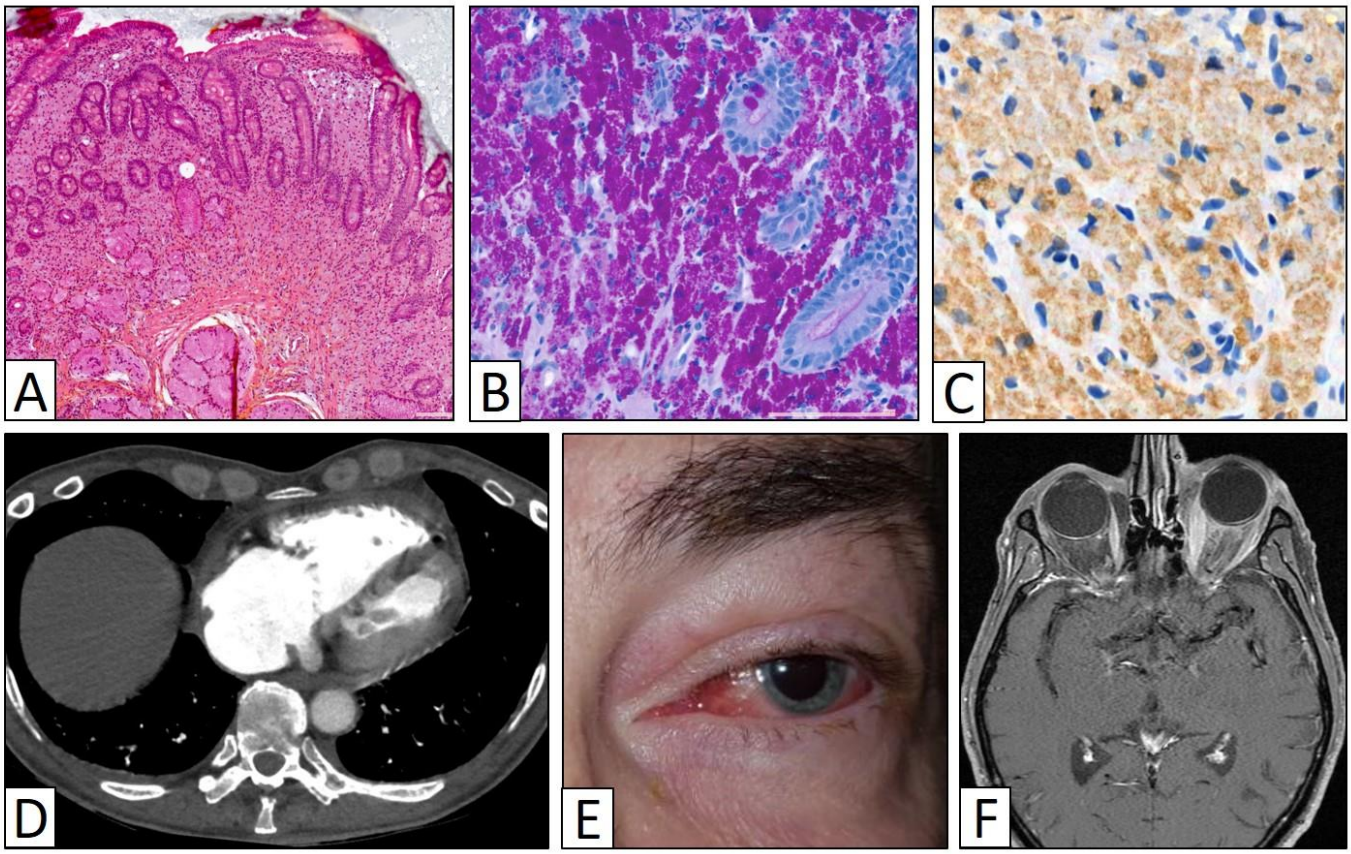

Figure 1. Main characteristics of the patient at the diagnosis of Whipple's disease

A. Diffuse and massive infiltration of the lamina propria by foamy and pink macrophages (Hemalun, Eosin and Safran [HES] x100)

B. PAS-positive macrophages with round bacterial inclusions in the lamina propria (periodic acid-Schiff [PAS] x200)

C. CD68-positive macrophages in the lamina propria (Agilent, clone PG-M1 1/200, x200)

D. Axial contrast-enhanced high-resolution computed tomography (HRCT) image of the mediastinum showing right atrium and ventricle dilation

E. Photograph showing the left congestive eye associated with proptosis, periorbital inflammation and lateral deviation

F. Orbital magnetic resonance imagery (MRI) in T2-weighted imaging showing left exophthalmia and a hypersignal of the left orbit consistent with an inflammatory pseudo-tumor