Reversible pulmonary hypertension associated with multivisceral Whipple's disease

To the Editor:

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 PCR on different biological samples [1]. Classical treatment requires prolonged antibiotic therapy and allows rapid improvement. Combination therapy with doxycycline and hydroxychloroquine over 1 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 1 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 haemodynamics 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-oesophageal reflux and systemic hypertension treated by beta-blockers, was hospitalised 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 kg, diarrhoea, 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 dyspnoea that had been worsening for a few weeks. Clinical examination showed signs of right heart failure, biology showed a microcytic anaemia and increased N-terminal pro-B-type natriuretic peptide (NT-proBNP), and transthoracic echocardiography showed dilation of the right heart chambers, increased estimated systolic pulmonary artery pressure (65 mmHg) and right ventricular dysfunction (tricuspid annular plane systolic excursion 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 catheterisation (RHC) confirmed severe precapillary PH without acute pulmonary vasodilator response to inhaled nitric oxide: mean pulmonary artery pressure (mPAP) 40 mmHg, cardiac output 3.1 $L \cdot min^{-1}$, cardiac index 2 $L \cdot min^{-1} \cdot m^{-2}$, pulmonary artery wedge pressure 13 mmHg and pulmonary vascular resistance (PVR) 8 WU. Treatment with intravenous dobutamine and diuretics was initiated together with oral dual combination of pulmonary arterial hypertension (PAH) drugs (bosentan and tadalafil). Evolution was favourable, 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, diarrhoea and microcytic anaemia, a gastroscopy was performed, and duodenal biopsies showed infiltration of the lamina propria by foamy PAS-positive macrophages (figure 1). As gastroscopy can be a high risk procedure in patients with PH, it was performed in the intensive care unit

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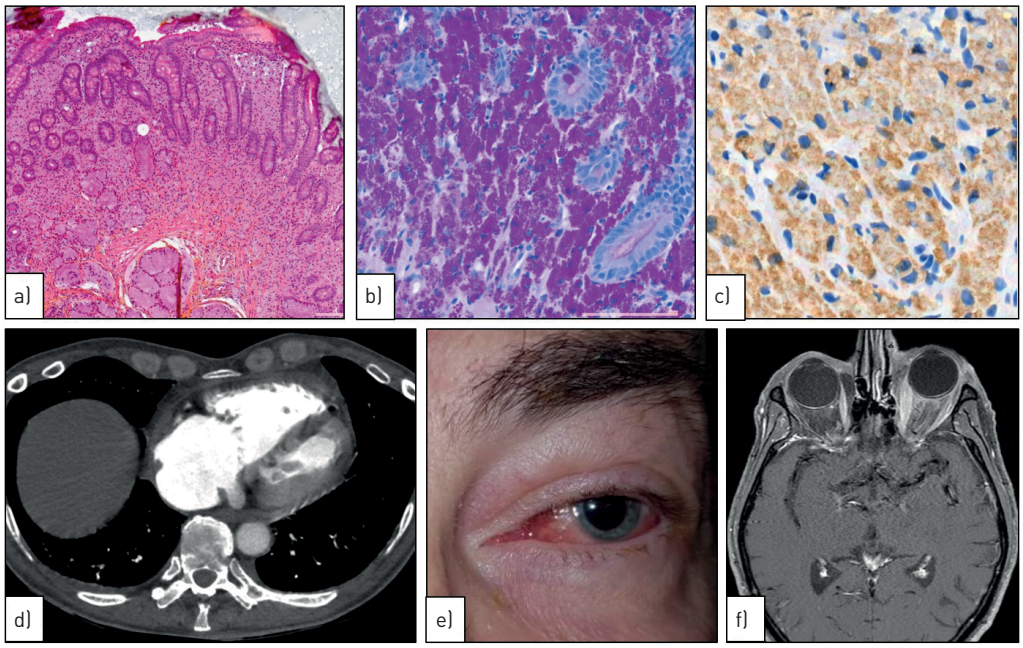

FIGURE 1 Main characteristics of the patient at the diagnosis of Whipple's disease. a) Diffuse and massive infiltration of the lamina propria by foamy and pink macrophages (haemotoxylin, eosin and safran, original magnification ×100). b) Periodic acid-Schiff-positive macrophages with round bacterial inclusions in the lamina propria (original magnification ×200). c) CD68-positive macrophages in the lamina propria (Agilent, clone PG-M1 1/200, original magnification ×200). d) Axial contrast-enhanced high-resolution computed tomography 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 in T2-weighted imaging showing left exophthalmia and a hypersignal of the left orbit consistent with an inflammatory pseudo-tumour.

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-tumour of the left orbit (figure 1). Doxycycline (100 mg twice per day) and hydroxychloroquine (200 mg three times per day) were started. After 2 months, the patient's evolution was remarkable: he experienced great improvements in his general state (weight gain of 13 kg in 9 months), with total correction of all initial symptoms. Repeated haemodynamic 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. 14 months after diagnosis and 5 months after interruption of PAH therapy, he had no exercise limitations in New York Heart Association functional class I, with 610 m 6-min walk distance and a peak oxygen uptake at 85% of the theoretical maximum (26.4 $mL \cdot kg^{-1} \cdot min^{-1}$), with normal biological markers, including NT-proBNP (141 $pg \cdot mL^{-1}$). C-reactive protein (CRP), which was 107 $mg \cdot L^{-1}$ at the diagnosis, remained <5 $mg \cdot L^{-1}$ during the follow-up. He continued on combined doxycycline and hydroxychloroquine for 1 year and will continue doxycycline for life to prevent WD relapses. He had no side-effects from the treatments, and repeated ECG 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 favourable 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 haemodynamic evolution after treatment was well documented by RHC in only two patients [7].

Our patient is the first reported case with favourable 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 haemodynamic outcomes with WD therapy argue in favour 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].

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