Whipple's disease-associated pulmonary hypertension with positive vasodilator response despite severe hemodynamic derangements

Salah Najm MD[1], Joud Hajjar MD[1], Robert P Nelson Jr MD[1,2], Ramana S Moorthy MD[3], Karen M Wolf MD[1,4], Tim Lahm MD[1,4,5]

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Pulmonary hypertension (PH) associated with Whipple's disease (WD-PH) is extremely rare, and the underlying pathophysiological processes are incompletely understood. Alterations in hemodynamics can be severe, with right ventricular (RV) dysfunction being common. A case involving a 23-year-old man with WD-PH who exhibited a dramatic vasodilator response during right heart catheterization despite severely altered pulmonary hemodynamics and concomitant RV dysfunction is reported. While the patient's symptoms responded poorly to treatment with nifedipine and sildenafil, significant improvement in dyspnea, RV dysfunction and pulmonary pressures were noted following antibiotic therapy. The present report highlights that despite severely elevated pulmonary artery pressures and RV dysfunction in WD-PH patients, a highly significant vasodilator response and dramatic improvement with antibiotic therapy may be observed. Furthermore, the case highlights the phenomenon of PH in the setting of inflammation, suggesting that adequate control of the inflammatory response can be accompanied by a marked improvement in hemodynamics in certain types of PH.

Key Words: *Cytokines; Hemodynamics; Inflammation; Right ventricular dysfunction;* Tropheryma whipplei

L'hypertension pulmonaire associée à la maladie de Whipple ayant une réponse vasodilatatrice positive malgré de graves perturbations hémodynamiques

L'hypertension pulmonaire (HP) associée à la maladie de Whipple (HP-MW) est d'une extrême rareté, et on n'en comprend pas complètement les processus physiopathologiques sous-jacents. Les altérations hémodynamiques peuvent être importantes, et la dysfonction ventriculaire droite (VD) est courante. Est présenté le cas d'un homme de 23 ans atteint d'HP-MW qui a présenté une réponse vasodilatatrice importante pendant un cathétérisme du cœur droit, malgré une grave perturbation de l'hémodynamique pulmonaire et une dysfonction VD concomitante. Les symptômes ont peu réagi aux traitements à la nifédipine et au sildénafil, mais la dyspnée, la dysfonction VD et les pressions pulmonaires se sont atténuées après l'antibiothérapie. Le présent rapport démontre que, malgré des pressions artérielles pulmonaires élevées et une dysfonction VD chez les patients atteints d'HP-MW, on peut observer une réponse vasodilatatrice hautement significative et une amélioration considérable à l'antibiothérapie. De plus, ce cas fait ressortir le phénomène de l'HP en présence d'inflammation, ce qui laisse supposer qu'un bon contrôle de la réponse inflammatoire peut s'accompagner d'une amélioration marquée de l'hémodynamique dans certains types d'HP.

Pulmonary hypertension (PH) secondary to Whipple's disease (WD-PH) is extremely rare. We report a case of WD-PH presenting with significantly altered hemodynamics and right ventricular (RV) dysfunction, yet exhibiting marked vasodilator responsiveness during right heart catheterization (RHC) and dramatic improvement with antibiotic therapy. PH-specific therapy alone did not have significant effects, suggesting that adequate control of the inflammatory response may be important in certain types of PH.

CASE PRESENTATION

A 23-year-old Caucasian man with presumed sarcoidosis (based on noncaseating granulomas on mediastinal lymphadenopathy; treated with 40 mg prednisone/day) presented with exertional dyspnea, hypotension and signs of RV failure. RHC revealed severe PH (Table 1) without evidence of a left-to-right shunt. Despite severely altered hemodynamics and RV dysfunction, the patient demonstrated a dramatic vasodilator response after administration of 40 ppm of nitric oxide (Table 1). Other causes of PH were ruled out. In particular, hepatitis and HIV serologies, connective tissue disease markers, thyroid function tests, urine drug screen, and hemolysis laboratory results were negative or within normal limits. A ventilation/perfusion scan did not reveal any evidence of chronic thromboembolic disease. There was no clinical evidence of sleep disordered breathing. A computed tomography (CT) scan of his chest did not suggest any evidence of parenchymal lung disease. Nifedipine (120 mg/day) and sildenafil (20 mg three times/day [added due to disease severity]) were started for presumed sarcoidosis-associated PH, and prednisone was continued. Dyspnea and edema improved only minimally. Six months later, the

TABLE 1
Hemodynamic studies and New York Heart Association class at diagnosis, after vasodilator challenge and after one year of antibiotic therapy

	January 2009		
January 2008	Pre NO	Post NO	August 2009
PAP, mmHg	102/47/66	47/9/27	45/15/27
RAP, mmHg	12	–	7
CO, L/min	5.5	6.9	5.35
PCWP, mmHg	5	5	10
PVR, Wood units	11	4	3.2
WHO functional class	III	–	I

CO Cardiac output (Fick method); NO Nitric oxide (40 parts per million); PAP Pulmonary artery pressure (systolic/diastolic/mean); PCWP Pulmonary capillary wedge pressure; PVR Pulmonary vascular resistance; RAP Right atrial pressure

[1]*Department of Medicine,* [2]*Division of Hematology/Oncology;* [3]*Associated Vitreoretinal and Uveitis Consultants Indianapolis, St Vincent Hospital Indianapolis, and Department of Ophthalmology;* [4]*Division of Pulmonary, Allergy, Critical Care and Occupational Medicine, and* [5]*Roudebush VA Medical Center; all at Indiana University School of Medicine, Indianapolis, Indiana, USA. Dr Najm's current affiliation is Department of Pulmonary and Critical Care Medicine, University Hospital Case Medical Center, Cleveland, Ohio, USA*

Correspondence: Dr Tim Lahm, 1481 West 10th Street, VA111P-IU, Indianapolis, Indiana 46202, USA. Telephone 317-988-3811, fax 317-988-3976, e-mail tlahm@iupui.edu

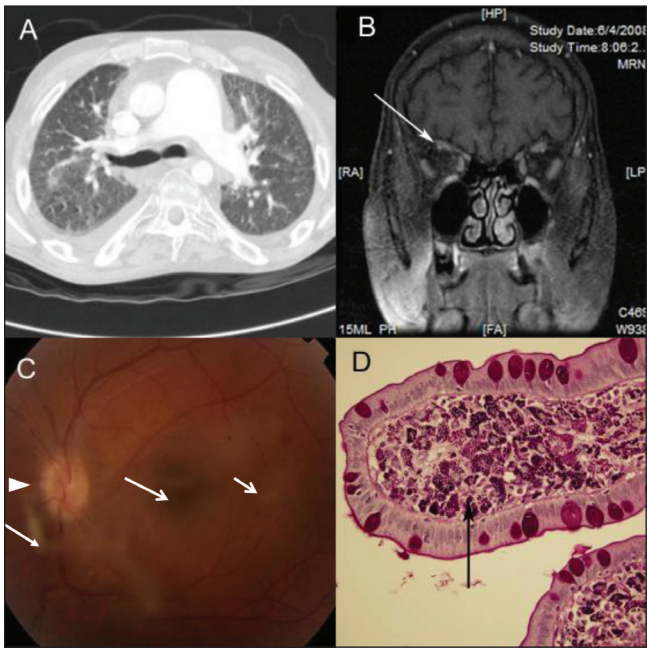

Figure 1) *Representative pathological findings observed in the patient.* **A** *Computed tomography scan of the chest showing a massively enlarged pulmonary artery (diameter 4.6 cm), small bilateral effusions and bilateral ground-glass infiltrates.* **B** *Magnetic resonance image of the brain showing right optic neuritis (arrow).* **C** *Colour fundus photographs of the left eye demonstrating intense vitritis with 'snowball-like' vitreous abscesses, optic disc edema (arrowhead), macular edema (long open arrow) and multiple small white choroidal* Tropheryma whipplei *abscesses in the posterior pole (short open arrow).* **D** *Duodenal biopsy with typical periodic acid-Schiff-positive stain for* T whipplei *in the mucosa (arrow) (original magnification ×20)*

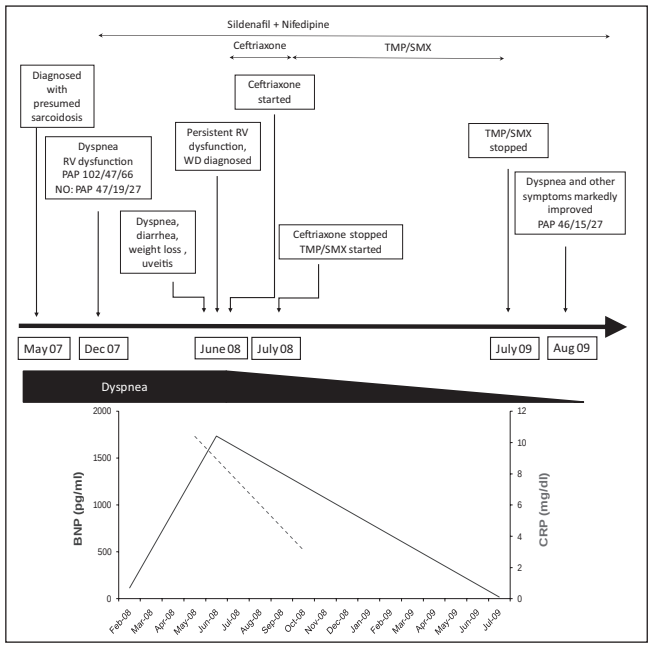

Figure 2) *Timeline of patient's clinical course, diagnostic interventions, biochemical parameters, and treatment. B-type natriuretic peptide (BNP) values (left x axis) are depicted as blue, uninterrupted line; C-reactive protein (CRP) values (right x axis) are depicted as red, dashed line. Apr April; Aug August; Dec December; Feb February; Jun June; NO Nitric oxide; Nov November; Oct October; PAP Pulmonary artery pressure (systolic/diastolic/mean [in mmHg]); RHC Right heart catheterization; RV Right venticular; Sep September; TMP/SMX Trimethoprim/sulfamethoxazole; WD Whipple's disease*

patient was admitted with worsening dyspnea, diarrhea, malnutrition, anemia, thoracic and abdominal lymphadenopathy, and severely reduced vision with bilateral panuveitis and macular edema. Chest CT revealed massive pulmonary artery dilation, ground-glass opacities, bilateral pleural effusions and a small pericardial effusion (Figure 1). Echocardiography demonstrated RV volume and pressure overload, with right atrial dilation, RV dilation, leftward shift of the interventricular septum and RV hypertrophy. The RV systolic pressure (RVSP) was estimated to be at least 65 mmHg to 70 mmHg. B-type natriuretic peptide level was markedly elevated (Figure 2). Left ventricular (LV) function was unremarkable, and there was no evidence of valvular heart disease. Esophagogastroduodenoscopy demonstrated diffuse inflammation and granular mucosal changes in the stomach and duodenum. Biopsies revealed periodic acid-Schiff (PAS)-positive macrophages (Figure 1). A presumptive diagnosis of WD was established and confirmed by direct peripheral blood and vitreous fluid polymerase chain reaction testing for *Tropheryma whipplei*. Intravenous ceftriaxone (2 g/day) was initiated for four weeks, followed by trimethoprim/sulfamethoxazole (160/800 mg/day) and rifampin (300 mg twice/day) for one year. Vasodilators were continued and prednisone was weaned. After initiation of antibiotic therapy, the patient's dyspnea and other symptoms improved dramatically. Repeat RHC one year later demonstrated significantly improved hemodynamics accompanied by improvements in functional class and biochemical parameters (Table 1, Figure 2). Vasodilators were subsequently discontinued, without any evidence of PH on follow-up echocardiography.

DISCUSSION

WD is caused by *Tropheryma whipplei*, a Gram-positive bacillus related to *Actinomycetes*. Infection occurs via the gastrointestinal route, resulting in extensive macrophage recruitment with subsequent engulfment of bacteria and production of proinflammatory cytokines (eg, interleukin [IL]-16 and IL-1β) (1). The inability to degrade bacterial antigens, potentially due to decreased IL-12 production and apoptosis of recruited macrophages, results in additional bacterial dissemination and multiorgan involvement (1). Symptoms are manifold and nonspecific (1). Our patient had several findings associated with WD (cognitive changes, seizures, liver dysfunction, malabsorption/diarrhea, optic neuritis/uveitis, thrombocytopenia/anemia, pleural effusions and noncaseating granulomatous mediastinal/abdominal lymphadenopathy). The diagnosis is established by PAS-staining of duodenal biopsies and direct testing for bacterial DNA in tissues or blood by polymerase chain reaction. Treatment consists of ceftriaxone or penicillin G in conjunction with streptomycin followed by trimethoprim/sulfamethoxazole for one to two years (1).

WD-PH is extremely rare, and is not listed in the recently revised classification of PH (2). Consequently, the association between WD and PH is not fully recognized. Proposed mechanisms include the consequences of a cytokine-mediated proinflammatory state, direct infiltration of the pulmonary vasculature by *T whipplei*, concomitant endocarditis/valvulopathy or pulmonary emboli with PAS-positive cells (3,4). The presence of pulmonary edema with normal LV function in our patient suggests a possible component of postcapillary PH (eg, pulmonary veno-occlusive disease – a condition associated with inflammatory PH [5,6]), or capillary leak from cytokine activation. Alternatively, it is conceivable that endocardial involvement may have been present, leading to heart failure and subsequent pulmonary edema. A transesophageal echocardiogram was not performed in this patient, but the presence of normal valvular appearance and function, as well as normal LV systolic and diastolic function on several high-quality transthoracic echocardiograms, makes this possibility less likely. Given the nonspecific findings on chest CT, it is difficult to identify a clear cause for the diffuse ground-glass opacities. Pulmonary veno-occlusive disease can occur despite the absence of pulmonary

edema after vasodilator challenge on RHC (7) and, therefore, remains a possibility in this case (especially because interstitial thickening was also observed), as does capillary leak or subtle endocardial involvement.

Our case is notable for several reasons. First, using the key words "Whipple's disease", "Whipple", "Tropheryma whipplei", "pulmonary hypertension" and "right heart failure" in various combinations in PubMed, only three reports of WD-PH were identified (3,4,8). While one study reported improvement with antibiotic therapy (4), and another study described improvement with calcium channel blockade (3), the marked acute vasodilator response observed in our patient – despite very high baseline pulmonary pressures and significant RV dysfunction – has not yet been described; indicating a favourable prognosis for WD-PH even if hemodynamic alterations are initially severe. We suspect that the significant inflammatory response seen in our patient elicited a marked vasoconstrictor response.

Second, our case highlights the phenomenon of PH in the setting of immune dysregulation, a condition speculated to be at the heart of WD (1). The association with an inflammatory state is of particular interest because proinflammatory mechanisms are known contributors to various forms of PH (9,10), sometimes causing severe PH and RV dysfunction. Mechanisms include direct infiltration with inflammatory and immunomodulatory cells, and cytokine-induced PA endothelial and RV myocyte dysfunction (9,10). Elevations in proinflammatory cytokine levels have been linked to survival in PH (11), which is of particular interest in light of the increased cytokine levels seen in patients with WD. Despite treatment with vasodilators and PH-specific therapy, our patient's PH did not improve until adequate antibiotic therapy was initiated, suggesting that adequate control of the inflammatory response may be of importance in the treatment of WD-PH. However, the etiological relationship between inflammation in WD and PH is poorly defined at this time and needs further investigation. Nevertheless, the impressive hemodynamic and clinical response to control of the WD-associated inflammatory state (reflected by decreasing C-reactive protein levels) (Figure 2) suggests that PH-specific therapy may not be required as first-line therapy in certain patient populations characterized by marked inflammation – a finding also described in connective tissue disease-associated PAH (12).

Third, our case stresses the importance of isolating the underlying cause of unexplained severe PH before costly and potentially dangerous PAH-therapy is initiated. In patients with unidentified multisystem disease, once connective tissue disease and sarcoidosis are ruled out, WD should be considered, especially given the therapeutic implications of making the diagnosis. WD can have striking similarities with sarcoidosis, including the presence of noncaseating granulomas on tissue biopsies (1), which led to the initial assumption of sarcoidosis in our patient. However, the diagnosis of sarcoidosis was refuted once the diagnosis of WD was made, a decision supported by the worsening of symptoms while the patient was on steroids and the ongoing improvement despite the prednisone wean.

Our investigation was limited by the lack of invasive hemodynamic assessment at the time of hospital admission (when the patient was on vasodilators, but not yet on antibiotics for WD). However, the significantly elevated RVSP, the echocardiographic and biochemical evidence of RV failure, and the lack of significant improvement in dyspnea or edema after inititation of vasodilator treatment suggested that the patient still had severe PH (and possibly even worsened RV failure) at the time of admission. RV dysfunction with a subsequent decrease in cardiac output would also explain the apparent decrease in RVSP compared with the hemodynamically measured pulmonary artery pressure six months previously, although we should caution against directly comparing these two measures because echocardiographic RVSP estimation may be unreliable in up to 50% of cases (13). Clinical symptoms, functional status and edema improved only after antibiotics were initiated, and this coincided with a decrease in plasma B-type natriuretic peptide values, a known marker of RV dysfunction in the absence of LV disease (14) (Figure 2), suggesting significant improvement in PH and RV dysfunction. This was confirmed by a repeat echocardiogram six weeks after the start of antibiotics, which revealed significant improvement in RV volume and pressure overload, and absence of septal shift. Unfortunately, a tricuspid regurgitant jet and, therefore, an estimation of RVSP, could not be obtained at that time.

CONCLUSION

WD-PH may present with discordant findings of significantly altered hemodynamics, yet manifest a dramatic response to vasodilators during RHC and significant improvement with antibiotics, potentially suggesting a strong inflammatory component. PAH-specific drugs may not be required as first-line therapy in this context.

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