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

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Pulmonary hypertension (PH) associated with 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, hypertension 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 computed tomography (CT) 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 par enchymal 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

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A 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 (BNP) values were markedly elevated (Figure 2). Left ventricular (LV) function was remarkable, 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 tapered. After initiation of antibiotic therapy, the patient’s dyspnea and other symptoms improved dramatically. Repeat RHC one year later demonstrated improved right heart function with normal RVSP (47/15/27 mmHg) and LV systolic and diastolic function (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 *Actinomyces*. 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/uvitis, 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 transthoracic echocardiogram was not performed in this patient, but the presence of normal valvar 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 intitial 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 vasocostrictor 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 initiation 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 D-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.

REFERENCES

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