JACC: CASE REPORTS VOL. 31, NO. 1, 2026

HEART FAILURE AND CARDIOMYOPATHIES

CLINICAL CASE

Severe Precapillary Pulmonary Hypertension Due to Whipple Disease

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ABSTRACT

BACKGROUND Whipple disease (WD), a rare systemic infection caused by *Tropheryma whipplei*, represents an uncommon but recognized cause of reversible pulmonary hypertension (PH).

CASE SUMMARY A 41-year-old woman with a history of arthritis, eczema, and low-grade fever was referred to our center with severe precapillary PH. Initial diagnostic work-up suggested sarcoidosis, prompting initiation of immunosuppressive therapy. Shortly thereafter, the patient developed severe diarrhea. Subsequent colonoscopy and intestinal biopsy revealed WD. After the initiation of targeted antibiotic therapy, the patient experienced rapid clinical improvement, with complete resolution of symptoms and normalization of hemodynamic parameters.

DISCUSSION This case demonstrates that systemic inflammation in WD can involve the pulmonary vasculature and lead to precapillary PH, which may be fully reversible with timely diagnosis and targeted antibiotic therapy.

TAKE-HOME MESSAGE PH is a pathophysiological condition defined by elevated mean pulmonary arterial pressure arising from primary pulmonary vascular disorders or as a consequence of other conditions such as WD. (JACC Case Rep. 2026;31:105939) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

HISTORY OF PRESENTATION

A 41-year-old woman without cardiovascular comorbidities initially presented to a local hospital with progressive dyspnea and fatigue after a recent episode of diarrhea and significant weight loss. She reported a marked reduction in exercise tolerance, as she was unable to climb 2 flights of stairs without stopping—an activity she had previously performed with ease. She was hospitalized twice. During the first admission, echocardiography revealed moderate to severe tricuspid regurgitation, right ventricular dysfunction, and an estimated systolic pulmonary artery pressure (PAP) of 70 mm Hg. High-resolution computed tomography (HRCT) of the chest showed enlarged mediastinal lymph nodes and septal line thickening. Right heart catheterization confirmed precapillary pulmonary hypertension (PH) with preserved cardiac index (right atrial pressure: 7 mm Hg, mean PAP: 24 mm Hg, pulmonary artery wedge pressure: 10 mm Hg, cardiac output: 5.3 L/min, cardiac index: 3.6 L/min/m^2, pulmonary vascular resistance: 2.6 Wood units, pulmonary artery saturation: 65%, systemic oxygen saturation: 99%). Inguinal lymph

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received July 3, 2025; revised manuscript received September 12, 2025, accepted October 3, 2025.

ISSN 2666-0849 https://doi.org/10.1016/j.jaccas.2025.105939

ABBREVIATIONS AND ACRONYMS

DL_{CO} = diffusing capacity of the lungs for carbon monoxide

HRCT = high-resolution computed tomography

IRIS = immune reconstitution inflammatory syndrome

K_{CO} = DL_{CO}-to-alveolar volume ratio

PAH = pulmonary arterial hypertension

PAP = pulmonary arterial pressure

PCR = polymerase chain reaction

PH = pulmonary hypertension

PVOD = pulmonary veno-occlusive disease

WD = Whipple disease

node biopsy revealed non-necrotizing granulomatous lymphadenitis, prompting initiation of steroid therapy and anakinra for suspected sarcoidosis. The patient was then readmitted with worsening dyspnea and signs of right heart failure. Diuretics and pulmonary arterial hypertension (PAH)-specific therapy with macitentan were started but were discontinued shortly thereafter owing to oxygen desaturation. Given the patient's worsening clinical status and ongoing desaturation despite targeted PAH-specific therapy with an Endothelin receptor antagonist, she was transferred to our pulmonary hypertension center for further evaluation.

PAST MEDICAL HISTORY

The patient had a history of seronegative arthritis, with symptomatic wrist involvement, eczema, and occasional low-grade fever, accompanied by persistent leukocytosis, thrombocytosis, and elevated erythrocyte sedimentation rate and C-reactive protein levels. The condition showed only partial response to multiple anti-inflammatory therapies, including hydroxychloroquine, corticosteroids, colchicine, and interleukin-1 receptor antagonists. In the months preceding admission at the local hospital, she also developed diarrhea and significant weight loss. A gastroenterological evaluation, including colonoscopy, revealed no abnormalities. Laboratory tests identified mild microcytic anemia, likely due to chronic inflammation, folate deficiency, and iron depletion.

TAKE-HOME MESSAGES

- Whipple disease can affect pulmonary vascular physiology and lead to precapillary pulmonary hypertension. Targeted antibiotic treatment resulted in full regression of precapillary pulmonary hypertension, with sustained hemodynamic normalization observed at the 10-month follow-up.
- Pulmonary hypertension is a pathophysiological condition defined by elevated mean pulmonary arterial pressure. It can arise from primary pulmonary vascular disorders or occur as a consequence of conditions such as Whipple disease.

DIFFERENTIAL DIAGNOSIS

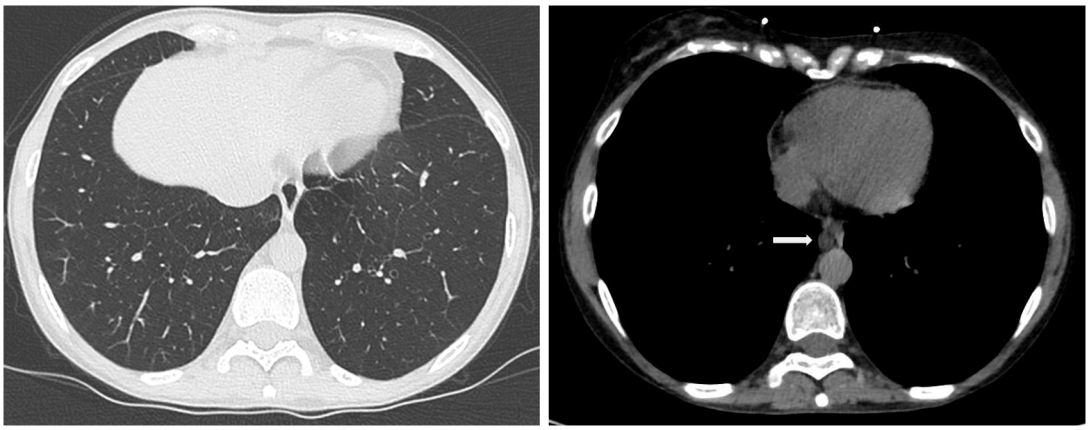
The patient's clinical presentation and diagnostic findings prompted consideration of several forms of precapillary PH within group 1 of the clinical classification.[1] PAH with features of venous/capillary involvement was strongly suspected, based on systemic desaturation during macitentan therapy and diffuse septal line thickening observed on HRCT. Additionally, mediastinal lymphadenopathy on HRCT and non-necrotizing granulomas found on inguinal lymph node biopsy raised concern for sarcoidosis. This condition may lead to PH through multifactorial and incompletely understood mechanisms, consistent with group 5 PH.

VISUAL SUMMARY **Timeline of Case Presentation**

Time	Events
Past symptoms and hospitalization	A 41-year-old woman with a history of arthritis, abdominal pain, eczema, and low-grade fever had previously been hospitalized twice for dyspnea and fatigue. During those admissions, she was diagnosed with PH, with a suspicion of PVOD in the context of sarcoidosis, based on non-necrotizing granulomas found in an inguinal lymph node biopsy.
Initial presentation	Patient presented with PH assessed as World Health Organization functional class III. RHC confirmed precapillary PH, and high-resolution computed tomography of the chest showed mild septal lines thickening, suggestive of PVOD. Diuretics and low-dose sildenafil were initiated, leading to mild symptom improvement.
10 d after presentation	Given the prior suspicion of sarcoidosis, an FDG-PET scan was performed, revealing increased uptake in the ileal loops, colon, and multiple lymph nodes. High-dose corticosteroids and methotrexate were started. Shortly after initiating immunosuppressive therapy, the patient developed severe diarrhea, marked anemia, and dehydration. Gastrointestinal endoscopy with biopsy led to the diagnosis of Whipple disease. Methotrexate was discontinued, corticosteroids tapered, and intravenous ceftriaxone was started, resulting in rapid resolution of symptoms. The patient was later transitioned to lifelong oral antibiotic therapy with trimethoprim-sulfamethoxazole.
2 mo after presentation	Marked clinical improvement followed. Predischarge RHC showed normalization of hemodynamic parameters, allowing discontinuation of sildenafil.
10 mo after presentation	The patient remained asymptomatic. Follow-up RHC confirmed sustained hemodynamic normalization both at rest and during exercise, with normal right atrial pressure.

FDG-PET = fluorodeoxyglucose positron emission tomography; PH = pulmonary hypertension; PVOD = pulmonary veno-occlusive disease; RHC = right heart catheterization.

FIGURE 1 Computed Tomography Scans Demonstrating Interlobular Septal Thickening With Slightly Enlarged Periaortic Lymph Nodes (Arrow)



INVESTIGATIONS

Transthoracic echocardiography showed a marked increase in the pressure gradient between the right ventricle and atrium (68 mm Hg), with minimal systolic straightening of the interventricular septum. HRCT confirmed mild interlobular septal thickening and slightly enlarged periaortic lymph nodes (Figure 1). Right heart catheterization confirmed precapillary PH, with a positive vasoreactivity test to nitric oxide, fulfilling European Society of Cardiology/European Respiratory Society (ESC/ERS) guideline criteria[1] (Table 1). Spirometry revealed a severe reduction in the diffusing capacity of the lungs for carbon monoxide (DL_{CO}) at 34%, with a similarly reduced value when corrected for alveolar volume (K_{CO}) at 37%. Given the suspicion of pulmonary veno-occlusive disease (PVOD), treatment with diuretic and low-dose sildenafil (5 mg 3 times daily) was initiated in place of calcium-channel blockers, resulting in mild clinical improvement. Given the biopsy finding of non-necrotizing granuloma, a total-body FDG-PET (fluorodeoxyglucose positron emission tomography) scan was performed (Figure 2). It revealed intense FDG uptake in the colon, ileal loops, and mesenteric lymph nodes. Based on these findings, high-dose corticosteroids and methotrexate were initiated. Shortly thereafter, the patient developed severe diarrhea and elevated fecal calprotectin levels (568 μg/mg; normal range 10-60 μg/g), leading to dehydration and severe cachexia. Upper and lower gastrointestinal endoscopy revealed duodenal lymphangiectasia, ileal inflammation, and focal colonic lesions (Figure 3). Histopathology identified foamy macrophages staining positive with periodic acid-Schiff staining (Figure 4), consistent with Whipple disease (WD). Methotrexate was promptly discontinued, and corticosteroids were tapered. Polymerase chain reaction (PCR) testing on intestinal biopsies confirmed the presence of *Tropheryma whipplei* DNA. Retrospective PCR analysis of the previously obtained inguinal lymph node biopsy also detected *T whipplei*, further confirming the diagnosis.

MANAGEMENT

Antibiotic therapy with intravenous ceftriaxone (2 g daily for 14 days) was initiated. Shortly thereafter, the patient developed fever, thrombocytopenia, and elevated inflammatory markers, consistent with immune reconstitution inflammatory syndrome (IRIS). Intravenous methylprednisolone 40 mg was administered, leading to rapid resolution of diarrhea and normalization of inflammatory parameters. After completing the 2-week course of ceftriaxone, treatment was transitioned to lifelong oral trimethoprim/sulfamethoxazole (800/160 mg twice daily), with continued corticosteroid therapy.

OUTCOME AND FOLLOW-UP

Follow-up transthoracic echocardiography showed a reduction in systolic PAP (40 mm Hg), and spirometry revealed a mild improvement of DL_{CO} (up to 44%)

TABLE 1 Hemodynamic Profile Before Diagnosis, After Initiation of Antibiotic Therapy, and After Starting Therapy

	Initial Presentation	1 mo After Presentation	4 mo After Presentation	10 mo After Presentation
BMI (kg/m^2)	19.3	18.9	21.4	23.4
HR (beat/min)	90	66	80	85
RAP (mm Hg)	8	8	10	7
s/d/m PAP (mm Hg)	61/20/34	29/12/19	32/14/24	29/11/19
s/d/m SAP (mm Hg)	110/70/83	115/75/91	137/95/112	119/87/100
PAWP (mm Hg)	7	12	14	11
PVR (Wood units)	6.1	1.8	2.0	1.5
CO (L/min)	4.4	3.9	4.9	5.5
CI (L/min/m^2)	3.1	2.8	3.3	3.5
SvO_2 AP (%)	64	68	76	75
SaO_2 (%)	100	99	97	99
Blocked pressure (mm Hg)	11	–	–	–
Transhepatic gradient (mm Hg)	3	–	–	–
HR (beats/min)	**75**	–	–	–
RAP (mm Hg)	**7**	–	–	–
s/d/m PAP (mm Hg)	**36**	–	–	–
s/d/m SAP (mm Hg)	**10**	–	–	–
PAWP (mm Hg)	**21**	–	–	–
PVR (Wood Units)	**8**	–	–	–
CO (L/min)	**4.7**	–	–	–
CI (L/min/m^2)	**3.3**	–	–	–
SvO_2 AP (%)	**67**	–	–	–
SaO_2 (%)	**99**	–	–	–
Therapy at the time of RHC	Prednisone 25 mg OD; anakinra 100 mg OD; pantoprazole 20 mg OD	Prednisone 60 mg OD; furosemide + spironolactone 25 mg/37 mg OD; sildenafil 5 mg TID; trimethoprim/sulfamethoxazole 800/160 mg BID	Prednisone 32.5 mg OD; trimethoprim/sulfamethoxazole 800/160 mg BID; cholecalciferol 10.000 IU/mL 6 drops OD; alendronate 70 mg wk; pantoprazole 20 mg OD	Prednisone 2.5 mg OD; trimethoprim/sulfamethoxazole 800/160 mg BID; furosemide + spironolactone 25/37 mg every other day; cholecalciferol 10.000 IU/mL 6 drops OD; alendronate 70 mg wk; pantoprazole 40 mg OD

Values after 5 minutes of inhalation of nitric oxide (26 ppm) are shown in **bold**.

BID = twice daily; BMI = body mass index; CI = cardiac index; CO = cardiac output; HR = heart rate; OD = once daily; PAP = pulmonary arterial pressure; PAWP = pulmonary artery wedge pressure; PVR = pulmonary vascular resistance; RAP = right atrial pressure; RHC = right heart catheterization; SaO_2 = arterial oxygen saturation; SAP = systemic arterial pressure; s/d/m = systolic/diastolic/mean; SvO_2 = mixed venous oxygen saturation; TID = 3 times daily.

and K_{CO} (48%). As right heart catheterization performed 1 month after presentation demonstrated a normal hemodynamic profile at rest, sildenafil was withdrawn. At discharge, the patient was asymptomatic with marked clinical improvement. At the 3-month follow-up, right heart catheterization showed a mild increase in biventricular filling pressures, attributed to a hyperkinetic and hypervolemic state likely related to high-dose corticosteroid therapy. By the 10-month follow-up, hemodynamics were normal both at rest and during exercise.

DISCUSSION

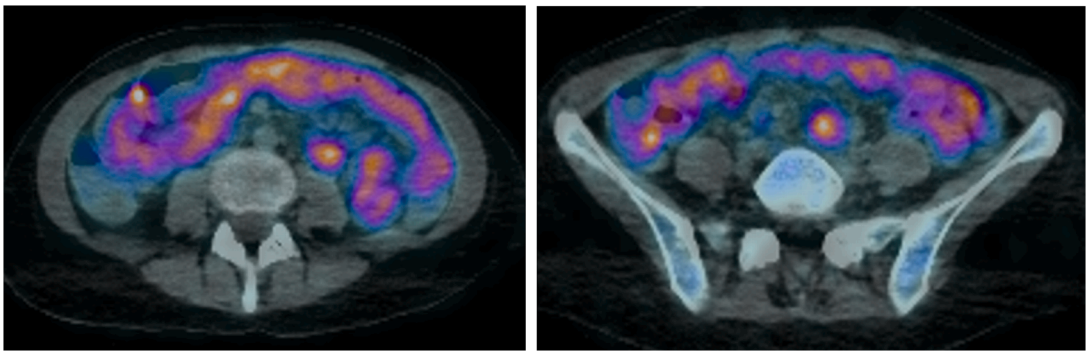
WD is a rare systemic infection caused by *T whipplei*, a Gram-positive bacillus first described by George Hoyt Whipple in 1907. The classic presentation includes diarrhea, malabsorption, weight loss, and arthralgia. Overall incidence is approximately 1 per million individuals, and it predominantly affects men (male-to-female ratio: 4:1) and occurs more frequently in populations with poor hygiene or occupational exposure (eg, sewer workers).[2]

The disease pathogenesis involves immune dysregulation, leading to systemic inflammation and tissue infiltration by infected macrophages. Diagnosis relies on the histological identification of PAS-positive macrophages in tissue biopsies and PCR confirmation of *T whipplei*. Standard treatment consists of a 2-week course of intravenous ceftriaxone or penicillin, followed by long-term oral trimethoprim/sulfamethoxazole.[2,3]

Although gastrointestinal and articular symptoms are common in WD, its association with PH is extremely rare. PH, defined by a mean PAP of >20 mm Hg on right heart catheterization, encompasses a broad spectrum of etiologies and is classified into 5 groups according to current ESC/ERS guidelines.[1]

The association between PH and WD is exceedingly rare, with only few cases documented in the

FIGURE 2 **Fluorodeoxyglucose Positron Emission Tomography Scans Revealing an Intense Fluorodeoxyglucose Uptake in the Colon, Ileal Loops, and Mesenteric Lymph Nodes**



literature.[4-7] Proposed mechanisms include cytokine-mediated vascular inflammation, direct vascular infiltration by *T whipplei*, and secondary effects from concurrent endocarditis or valvular disease.[8,9] Most reported cases describe a precapillary PH pattern with variable response to vasoreactivity testing and limited efficacy of PH-specific therapies.[6]

In our case, the patient displayed precapillary PH, with radiological signs suggestive of PVOD. Despite a positive vasoreactivity test, we opted for low-dose sildenafil rather than calcium-channel blockers given the patient's hypotension and the concern for PVOD, which can be aggravated by aggressive vasodilation. Notably, Pankl et al[4] and Camboulive et al[5] described similar cases of PH associated with WD that showed no acute vasoreactivity and that were managed with dual PAH-targeted therapy (bosentan and tadalafil), which were later withdrawn after clinical improvement. Our case, consistent with previous reports, describes the resolution of PH after antimicrobial therapy, providing strong evidence for the direct causal role of *T whipplei*. In our patient, the initial working diagnosis of sarcoidosis led to immunosuppressive therapy, which likely suppressed host defenses and unmasked the underlying infection. Similarly, Najm et al[6] reported a case where corticosteroid treatment, initiated under the assumption of sarcoidosis-associated PH, precipitated the emergence of overt WD.

Another important clinical feature in our patient was the development of IRIS, a recognized WD complication occurring after antibiotic therapy. IRIS reflects a dysregulated inflammatory response due to abrupt restoration of immune activity, and *T whipplei* is a known trigger. Cohort studies report IRIS in 10% to 20% of WD patients, with higher risk in

FIGURE 3 **Hyperemic Areas With Hypertrophic and Dyschromic (Whitish) Appearance of the Ileal Villi, Suggestive of Whipple Disease**

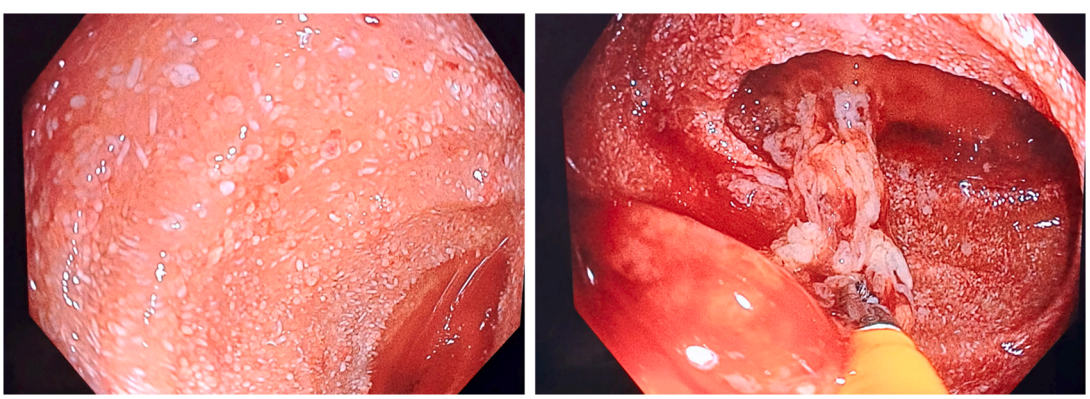
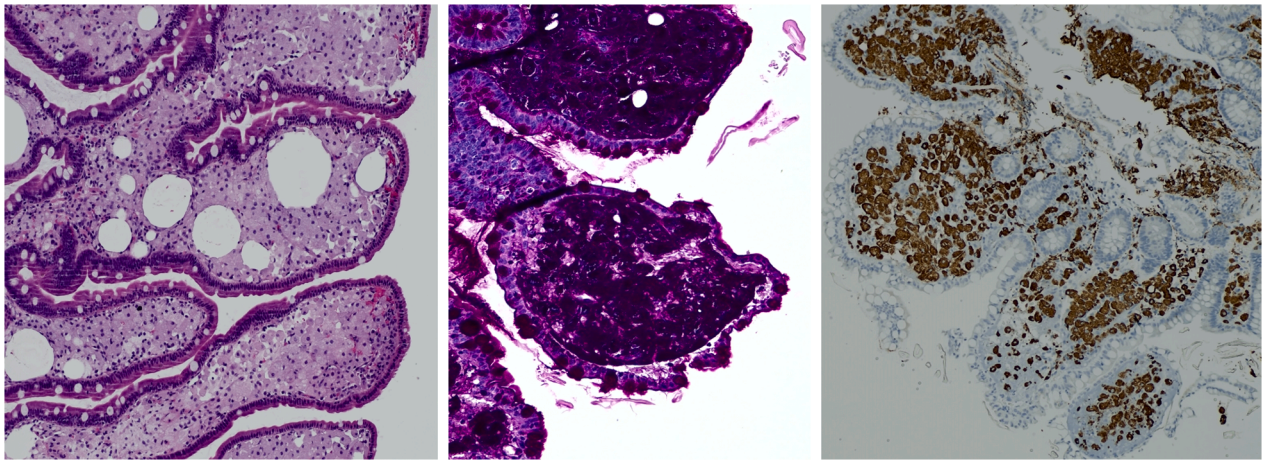


FIGURE 4 Duodenal Mucosal Biopsy Fragments



Biopsy fragments showed enlarged villi with irregular contours due to numerous macrophage-like elements with granular cytoplasm, strongly positive with periodic acid-Schiff (PAS) staining, resistant to diastase digestion, and immunoreactive for CD68. (Left) Hematoxylin & eosin, (Middle) PAS diastase, and (Right) CD68 immunohistochemistry.

those previously treated with immunosuppressants.[10] Although the clinical course is often mild, severe or even fatal cases have been described. Symptoms are varied and may include fever, arthritis, pleuritis, erythema nodosum, orbital inflammation, bowel perforation, or central nervous system involvement. Diagnosis is clinical, requiring high suspicion, and treatment typically involves corticosteroids, although steroid-refractory forms have been reported.

Our case reinforces the hypothesis that systemic inflammation from WD can extend to the pulmonary vasculature and induce precapillary PH.[5] The striking resolution of symptoms and normalization of hemodynamics after antibiotic treatment confirms the potential reversibility of this condition when properly diagnosed and managed. However, diagnosis remains challenging and requires careful assessment of clinical history and symptoms, along with a thorough evaluation of alternative etiologies.

EQUIPMENT LIST

Imaging
- CT scanner (Philips ICT 128)
- Echocardiograph (Philips Healthcare Affiniti CVx)
- PET/CT scanner Discovery MI (GE Medical Systems)

Catheterization
- Swan-Ganz catheter (Edwards Lifesciences) - thermodilution catheter (7 F, 110 cm)
- Guidewire 0.025-inch (0.64 mm)
- Introducer 8 F (2.7 mm)

CT = computed tomography; PET = positron emission tomography.

CONCLUSIONS

This case highlights a rare but reversible cause of precapillary PH associated with WD. Despite initial diagnostic challenges, PH resolved completely with targeted antibiotic therapy, supporting an underlying inflammatory pathogenesis. Recognizing WD as a potential etiology of PH is essential, particularly in patients presenting with systemic symptoms. Further studies are needed to confirm this association and validate the reversibility of PH with appropriate antimicrobial treatment.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Dardi has received grants, personal fees, and nonfinancial support from Janssen Pharmaceutica and Chiesi Farmaceutici. Prof Galiè has received grants, personal fees, and nonfinancial support from Janssen Pharmaceutica and Ferrer. Prof Palazzini has received grants, personal fees, and nonfinancial support from Janssen Pharmaceutica. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS **acute heart failure, pulmonary circulation, pulmonary hypertension, right-sided catheterization, right ventricle**