

Severe pulmonary hypertension reversed by antibiotics in a patient with Whipple's disease

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Abstract

The case is described of a 58 year old man with systemic Whipple's disease with pericardial and pleural effusions and severe pulmonary hypertension. After three months of antibiotic treatment there was a complete resolution, not only of the symptoms known to be associated with Whipple's disease (diarrhoea, arthralgia, pericardial and pleural effusions), but also of pulmonary hypertension.

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Whipple's disease is characterised by weight loss, diarrhoea, arthralgia, and abdominal pain.¹ Although the main manifestation of this disease is gastrointestinal, it is a systemic disorder and pulmonary involvement is a frequent but not well known finding. A chronic non-productive cough, dyspnoea, and pleuritic chest pain have been reported more often than pleural effusion and nodular shadowing.^{2,3}

Pulmonary hypertension associated with Whipple's disease has been reported previously in only two cases.^{4,5} We describe a case of systemic Whipple's disease with pericardial and pleural effusions and severe pulmonary hypertension in a 58 year old man in whom the pulmonary hypertension resolved completely after antibiotic therapy.

Case report

A 58 year old man was admitted with pericardial and pleural effusions and pulmonary hypertension of unknown origin. Three month before admission he had complained of diarrhoea and reported 6-10 bulky stools per day, a weight loss of 10 kg, progressive dyspnoea, and a dry cough. Physical examination showed a cachectic man (172 cm, 57.5 kg) with brownish hyperpigmentation. Cardiac examination revealed normal first and second heart sounds with a pansystolic 3/6 murmur over the tricuspid valve. The lungs showed dullness to percussion and absence of breath sounds at both bases. Bilateral pretibial oedema was present. The laboratory haematological values re-

vealed microcytic, hypochromic anaemia and blood chemical values indicated malabsorption (sodium 128 mmol/l; potassium 3.8 mmol/l; chloride 87 mmol/l; calcium 1.97 mmol/l; protein 54.7 g/l; albumin 27.5 g/l; cholesterol 93 mg/100 ml; alkaline phosphatase 212 U/l).

Gastroduodenoscopic examination, performed because of the diarrhoea, weight loss and laboratory findings indicating malabsorption, showed that the duodenal mucosa was coated with yellow-white plaques. The histological tissue specimen showed periodic acid Schiff (PAS) positive macrophages in the lamina propria and electron microscopy demonstrated intracellular bacilli. Furthermore, the species-specific base sequence for *Tropheryma whippelii*, demonstrated by polymerase chain reaction (PCR),⁶ confirmed the diagnosis of Whipple's disease.

A chest radiograph revealed small bilateral pleural effusions. High resolution computed tomographic (HRCT) scans of the chest showed perihilar areas of ground glass opacities, thickening of the interlobular and intralobular septa predominantly in the periphery of both lungs, and bilateral pleural effusions in the posterior basal area of both lungs measuring approximately 2 cm in diameter.

A diagnostic thoracentesis was performed and revealed an exudate. The Ziehl-Neelsen stain and cytological examination of the pleural fluid were non-diagnostic. However, in cells from pleural effusions *Tropheryma whippelii* specific amplification products were found by PCR.⁷

Transthoracic echocardiography (TTE) showed a dilated right ventricle and atrium. The interventricular septum was flattened, indicating increased right ventricular pressure or volume overload. Contrast echocardiography showed no evidence of intracardiac right-to-left shunt. An anterior small pericardial separation between pericardium and epicardium of approximately 2 cm in diastole was found. Colour flow Doppler sonography revealed tricuspid regurgitation with a regurgitant jet encompassing more than two thirds of the right atrium. The measured velocity of the regurgitant jet was 3.8 m/s, from which the estimated systolic gradient was calculated to be 57 mmHg using the modified Bernoulli equation ($P = 4V^2$). Thus, a right ventricular systolic pressure of at least 65 mmHg was estimated.

A ventilation-perfusion scan of the lungs revealed a very low probability of pulmonary embolism, since a small matched defect in the posterior basal area of the right lung was seen corresponding to the small amount of pleural effusion. No segmental or subsegmental mismatch was identified. Pulmonary function data indicated a mild restrictive ventilatory pattern (table 1) and a reduction in the carbon monoxide transfer factor (TLCO). Blood gas analysis revealed normoxaemia at rest, deteriorating during exercise, again indicating diffusion impairment (table 2).

Tests for antinuclear antibodies and their subsets, rheumatoid factor and antineutrophil cytoplasmic antibodies were negative as were all tests for HIV and other viral diseases.

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Table 1 Pulmonary function variables (before and three months after starting antibiotic therapy)

Variable	Before		After	
	Absolute	% predicted	Absolute	% predicted
TLC (l)	5.08	88%	5.60	91%
VC (l)	2.40	56%	3.37	79%
FEV ₁ (l)	1.50	44%	2.11	61%
FEV ₁ %VC	78%		78%	
TLCO	3.91	43%	5.89	65%

TLC = total lung capacity; VC = vital capacity; FEV₁ = forced expiratory volume in one second; FEV₁%VC = forced expiratory volume in one second as percentage of vital capacity; TLCO = carbon monoxide transfer factor.

Table 2 Blood gas analysis (before and three months after starting antibiotic therapy)

Blood gas	Rest		Exercise	
	Before	After	Before	After
Pao ₂ (mmHg)	77	89	68	93
Paco ₂ (mmHg)	32	37	28	37
A-aDo ₂ (mmHg)	33	15	46	12

Pao₂ = arterial oxygen tension; Paco₂ = arterial carbon dioxide tension, A-aDo₂ = alveolar-arterial difference in Po₂.
1 kPa = 7.5 mmHg.

After the diagnosis of Whipple's disease had been established, antibiotic therapy was started with penicillin G and gentamicin intravenously for 10 days followed by trimethoprim and sulphamethoxazole orally twice daily for one year. After beginning antibiotic treatment the diarrhoea resolved completely, the general condition of the patient improved, he started to gain weight, and the laboratory haematological values became normal. Three months after starting antibiotic therapy gastroduodenoscopic examination showed a markedly improved duodenal mucosa and increased jejunal folds. A biopsy sample of the duodenal tissue showed fewer PAS positive macrophages than at the initial examination.

A CT scan of the chest revealed complete resolution of the bilateral pleural effusions, the ground glass opacities, and the thickening of the interlobular and intralobular septa. Trans-thoracic echocardiography showed a right ventricle and atrium of normal size with no pericardial effusion. The maximum velocity of the tricuspid regurgitant jet was 2.2 m/s, indicating a pulmonary artery pressure within normal limits.

The pulmonary function data at that time showed that the total lung capacity and the carbon monoxide transfer factor per lung area were normal (table 1). Blood gas analysis revealed normoxaemia at rest and during exercise (table 2).

Discussion

Although involvement of the lung as a site of this disease was reported in Whipple's first description in 1907,¹ it is now known that the lung and the pleura may be affected both before and after the development of diarrhoea.³

The finding of severe pulmonary hypertension in Whipple's disease, however, has been reported in only two cases in the literature, in one as a result of severe aortic insufficiency and in the other by chronic progressive aortic regurgitation. Endocarditis, caused by *Tropheryma whippelii*, was thought to be the cause. Evidence of pericardial and endocardial involvement in Whipple's disease has been reported previously.⁸ In our patient involvement of the pericardium was evident because of the pericardial effusion.

The pulmonary function parameters demonstrated a slight restrictive ventilatory pattern and a reduced carbon monoxide transfer factor, possibly caused by the small amounts of bilateral pleural effusions and the thickening of the alveolocapillary membrane as shown by HRCT scanning. Both the small bilateral pleural effusions and the thickening of the interlobular and intralobular septa caused only mild functional impairment and cannot explain the severity of this pulmonary hypertension.

The strongest evidence for a causal relationship between Whipple's disease and pulmonary hypertension in our patient, however, was the resolution of the pulmonary hypertension after antibiotic therapy. It is therefore reasonable to assume that pulmonary vascular involvement by *Tropheryma whippelii* was the cause of pulmonary hypertension in this case.

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