Histopathology and Exercise: A Winning Combination in Pulmonary Fibrosis: A Case Report

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The diffuse parenchymal lung diseases form a heterogeneous group of disorders characterized by varying degrees of inflammation and fibrosis involving the space between epithelial and endothelial basement membranes. Among the diffuse parenchymal lung diseases of unknown etiology, one of the most common is usual interstitial pneumonia/idiopathic pulmonary fibrosis, which carries the worst prognosis. In contrast, nonspecific interstitial pneumonia, which belongs to the same diffuse parenchymal lung disease group, has a more favorable prognosis. Based on the relative amount of inflammation and fibrosis observed on lung biopsies, at least 2 nonspecific interstitial pneumonia patterns have been suggested: cellular and fibrosing. The long-term prognosis is excellent for patients with nonspecific interstitial pneumonia with a cellular pattern, as compared to patients with a fibrosing pattern. We describe here a patient with nonspecific interstitial pneumonia with a fibrosing pattern in a highly practiced runner, showing an unexpectedly long-term favorable course, and consider the possible role of exercise in the diagnosis and clinical course of the disease. This case reinforces the evidence that exercise training, which is a principal component of pulmonary rehabilitation, may have clinically important effects on functional exercise capacity, especially if it is delivered early in the course of the disease. *Key words: diffuse parenchymal lung diseases; non-specific interstitial pneumonia; exercise; pulmonary rehabilitation.* [Respir Care 2014;59(3):e31–e34. © 2014 Daedalus Enterprises]

Introduction

The diffuse parenchymal lung diseases are a heterogeneous group of more than 200 separate disorders characterized by varying degrees of inflammation and fibrosis involving the space between the epithelial and endothelial basement membranes,[1] or, as occurs in a small number of diseases, by alveolar filling.[1,2]

Recently, diffuse parenchymal lung diseases have been classified into 4 categories, based on whether the cause is known.[2] The idiopathic interstitial pneumonias form a subgroup of diffuse parenchymal lung diseases of unknown etiology. The American Thoracic Society/European Respiratory Society 2002 Consensus Classification Statement subdivided idiopathic interstitial pneumonias into 7 clinical, radiologic, and pathologic entities.[3] Among the different types of idiopathic interstitial pneumonias, one of the most commonly encountered is usual interstitial pneumonia/idiopathic pulmonary fibrosis, which carries the worst prognosis, with a median survival of 2.5–3.5 years.[4] In contrast, nonspecific interstitial pneumonia has a more favorable prognosis.[5] It can be idiopathic or associated with connective tissue diseases or environmental exposure. Based on the amount of inflammation and fibrosis observed on lung biopsies, there are 2 nonspecific interstitial pneumonia patterns: cellular and fibrosing.[6] The long-term prognosis is excellent for patients with nonspecific interstitial pneumonia with a cellular pattern, as compared to patients with a fibrosing pattern, who mostly die within 10 years of diagnosis. Honeycombing on high-resolution computed tomography (HRCT) is a predictor of poor outcome.[7]

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Table 1. Evolution of Pulmonary Function Test Results in a Patient With Nonspecific Interstitial Pneumonia With Fibrosing Pattern

	Baseline 2006	At Admission 2010	After Rehabilitation 2010	Present 2012
FVC, L	4.32	2.77	3.60	3.44
FVC, % predicted	105	68	89	81
FEV_1, L	3.43	2.45	2.97	2.84
FEV_1, % predicted	101	75	92	91
FEV_1/FVC	0.78	0.88	0.82	0.82
TLC, L	6.10	3.56	4.46	4.41
TLC, % predicted	93	54	68	67
$D_{LCO}/\dot{V}_A$, mL/min/mm Hg	4,040	1,940	2,130	2,300
$D_{LCO}/\dot{V}_A$, % predicted	73	46	51	55
P_{aO_2}, mm Hg	81	51	67	68

TLC = total lung capacity
D_{LCO} = diffusing capacity of the lung for carbon monoxide
$\dot{V}_A$ = alveolar volume

Table 2. Evolution of Exercise Test Results in a Patient With Nonspecific Interstitial Pneumonia With Fibrosing Pattern

	Baseline 2006	At Admission 2010	After Rehabilitation 2010	Present 2012
6-min walk test results				
S_{pO_2}, %				
Baseline	98	98	97	97
End	96	88	92	90
Distance, m	663	295	354	383
Final Borg dyspnea score	1.5	7	2	3
Cardiopulmonary exercise test results (only conducted at baseline)				
Peak $\dot{V}_{O_2}$, % predicted	61			
Maximum $\dot{V}_{O_2}$ at anaerobic threshold, mL/min (normal 60–85)	57			
$\dot{V}_{O_2}$/heart rate, % predicted	63			
P_{aO_2}, mm Hg				
Baseline	81			
Final	69			

$\dot{V}_{O_2}$ = oxygen uptake

We describe here a case of nonspecific interstitial pneumonia with a fibrosing pattern in a highly practiced runner who had an unexpectedly long-term favorable course, and consider the possible role of exercise in the clinical course of the disease.

Case Report

In July 2006, a 50-year-old white man presented to us with non-productive cough and dyspnea, which had recently started and were accentuated by exercise. He had no fever, chest pain, hemoptysis, weight loss, nor appetite loss. He was a smoker (35 pack-years) and had a family history of COPD and high blood pressure. He worked as land surveyor and had an unremarkable medical history. He was a highly practiced runner, who ran 8 km, in 1 hour, 4 times a week. He had no pets at home, especially birds, and no past asbestos exposure. Physical examination disclosed bilateral finger clubbing and post-tussive "Velcro" crackles at both lung bases.

Laboratory studies revealed elevated erythrocyte sedimentation rate (37 mm/h, normal value $<$ 15 mm/h) and C-reactive protein (13.7 mg/L, normal range 0–5 mg/L), but rheumatoid factor, anti-nuclear antibodies, anti-neutrophilic cytoplasmic antibodies, double-stranded DNA antibodies, and extractable nuclear antigens were all in the normal range.

His baseline pulmonary function test results were all in the normal range (Table 1). In a 6-min walk test he walked 663 m, at the end of the test his Borg dyspnea score was 1.5, and he had no important S_{pO_2} decrease during the test (Table 2). But in a maximal cardiopulmonary exercise test he had a substantial P_{aO_2} decrease, from 81 to 69 mm Hg (see Table 2).

HRCT showed increased peripheral reticular markings, especially at the lung bases, with honeycombing and diffuse thickening of the alveolar septa.

Bronchoscopy was unremarkable. Bronchoalveolar lavage fluid revealed no malignant cells, and a CD4/CD8 T lymphocytes ratio of 0.9 (range 1.3–2.3). The bronchoalveolar lavage fluid was negative on both microscopy and culture for bacteria, fungi, and mycobacterium. Surgical biopsy of the right upper and lower lobe showed predominant features of nonspecific interstitial pneumonia, with a rather uniform fibrosing pattern and associated lymphoid follicles, but without fibroblastic foci.

On the basis of the laboratory, histopathology, and radiologic results, the diagnosis was nonspecific interstitial pneumonia with fibrosing pattern. We promptly initiated oral prednisone: 1 mg/kg of body weight, daily for 12 weeks, then tapered over 6 weeks, then stopped. There were no important adverse effects.

After the first few weeks of treatment he experienced marked improvement in cough and exercise dyspnea, resumed his exercise training, and within a few months reached almost the same intensity exercise he had before the symptoms arose. HRCT 6months after the end of treatment was substantially unchanged, and showed only mild ground-glass attenuation and patchy consolidation.

In December 2010, following 4 years of well-being, during which he continued his usual exercise training, he presented with persistent cough, severe dyspnea at rest, and fever, and urgently hospitalized. On admission laboratory blood tests showed neutrophilic leucocytes and elevated erythrocyte sedimentation rate (56 mm/h) and C-reactive protein (226 mg/dL). Pulmonary function tests revealed a moderate restrictive defect, a severe reduction in diffusing capacity of the lung for carbon monoxide, and severe hypoxemia. Blood gases analysis showed metabolic alkalosis (pH 7.48, P_{CO_2} 38.5 mm Hg, HCO_3 27.9 mmol/L) (see Table 1). His 6-min walk test was 295 m and during the test he desaturated from 89% to 81% (see Table 2).

Doppler echocardiography demonstrated enlargement of the right atrium and ventricle, with a systolic right ventricular pressure of 45 mm Hg. Left ventricular systolic and diastolic function was in the normal range.

HRCT chest revealed increased reticular markings, widespread bilateral, asymmetrical patchy areas of ground glass attenuation with basal predominance, and thickened bronchovascular bundles in the basal fields of both lungs.

The diagnosis was exacerbation of nonspecific interstitial pneumonia, and he was started on intravenous glucocorticosteroids (methylprednisolone, 5 mg/kg daily), intravenous antibiotics (meropenem, voriconazole, and levofloxacin), intravenous diuretics, and oral N-acetylcysteine.

After 2 weeks the exacerbation resolved and he began a 5-week pulmonary rehabilitation program, including respiratory-muscle exercise training and upper and lower limb muscle training. Daily sessions included low-weight, high-repetition arm cycle ergometer training (30 min), treadmill walking (30 min), and bicycle training (30 min). He also attended 1-hour educational classes 3 times a week. After rehabilitation he had consistent improvements in symptoms, lung function, and exercise tolerance (see Table 1), and since December 2012 (as assessed via periodic telephone interviews) he has been asymptomatic at rest and continues his exercise, walking 1 hour a day, 3 times a week, with supplemental oxygen at 1 L/min, although, as would be expected, at a lower intensity than before the symptoms arose.

Discussion

Nonspecific interstitial pneumonia, described by Katzenstein and Fiorelli in 1994, is now considered a distinct clinical entity, with peculiar clinical, radiologic, and pathologic features that distinguish it from other idiopathic interstitial pneumonias.[6]

Histopathologically, nonspecific interstitial pneumonia is characterized by a temporally uniform interstitial pneumonia, in contrast to the temporal heterogeneity observed in usual interstitial pneumonia.[6,8] Moreover, the fibroblast foci typically observed in usual interstitial pneumonia are rarely seen in nonspecific interstitial pneumonia.[9] On HRCT, ground-glass opacities, reticular abnormalities, and traction bronchiectasis are frequently seen, and are typically bilateral and symmetrical, with lower-lobe predominance, whereas honeycombing is generally absent and if present is not the predominant radiographic abnormality.[10]

The natural course of nonspecific interstitial pneumonia has not completely been elucidated,[11] but, in general, these patients have a substantial response to glucocorticosteroids; in particular the cellular pattern responds better than does the fibrosing pattern.[12] Thus, the prognosis of patients with the cellular pattern of nonspecific interstitial pneumonia is excellent,[10] compared to patients with the fibrosing pattern, which has the same ~5-year survival rate as usual interstitial pneumonia.[7]

Our patient presents some peculiarities. First, it was probably his high level of physical activity that enabled us to make an early diagnosis of nonspecific interstitial pneumonia. In fact, exercise dyspnea and cough, which are the typical symptoms of diffuse parenchymal lung diseases, initially occurred in our patient exclusively in association with high-intensity exercise, and therefore we probably saw him earlier than if he had had a sedentary lifestyle.

The initial lung function tests showed no important abnormalities compatible with the diagnosis of diffuse parenchymal lung disease, except for a modest reduction in diffusing capacity of the lung for carbon monoxide. In particular, the 6-min walk test showed no desaturation, probably because this test just reflects an exercise capacity sufficient for the usual activities of daily living. Instead, in this fit patient the maximal cardiopulmonary exercise test was necessary to identify desaturation.

Following diagnosis and initial treatment with high-dose oral glucocorticosteroids, the disease remained stable from 2006 through 2010, when he had a severe exacerbation.

Despite the favorable 5-year survival rate of 74%, one study found that patients with fibrosing nonspecific interstitial pneumonia were frequently hospitalized, had a recurrence rate of 36%, and the interval between completion of initial treatment and recurrence was 11.6 ± 14.1 months.[13] Moreover the extent of ground-glass opacities on initial HRCT correlated well with serial changes of lung function, and the presence of honeycombing was strongly associated with poor prognosis.[13] In our patient, despite radiologic findings that would suggest poor prognosis (honeycombing and fibrosing pattern), he had a 4-year period of stability, during which, despite progressive worsening of the HRCT findings, he was able to continue high-level exercise.

Several factors probably contributed to the preservation of our patient's exercise capacity: optimal baseline pulmonary function; the diagnosis was made during a non-exacerbation phase of the disease; and probably favorable

influence of his regular high-level exercise. Although exercise is generally recognized to have a role in exacerbation-prevention in many chronic respiratory disorders,[14,15] in particular in COPD,[16] the role of pulmonary rehabilitation in patients with diffuse parenchymal lung diseases is less well known. In fact, the pulmonary rehabilitation guidelines only recommend low-level exercise for patients with diffuse parenchymal lung diseases.[17,18]

In contrast to those recommendations, evidence is now accumulating that pulmonary rehabilitation can result in clinically relevant improvements in patients with diffuse parenchymal lung diseases, although the improvements may differ greatly, depending on the diagnosis. Idiopathic pulmonary fibrosis, for instance, seems to be less responsive to pulmonary rehabilitation than are the other diffuse parenchymal lung diseases.[19]

Physical deconditioning might hasten the progression of diffuse parenchymal lung diseases, as happens in chronic lung diseases for which the advantages of pulmonary rehabilitation are well known.[16] An urgent research question is when pulmonary rehabilitation should begin in patients with diffuse parenchymal lung diseases. Our patient's experience suggests that vigorous exercise training may have clinically important effects on functional exercise capacity, especially if it is begun early in the course of the disease.

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