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Histopathology and exercise: a winning combination in pulmonary fibrosis. Report of a case

Viviana Pisano MD, Salvatore Fuschillo MD, Giovanni Balzano MD.

Pulmonary Rehabilitation Unit, Salvatore Maugeri Foundation, Scientific Institute of Telese, Telese Terme (BN), Italy

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Abstract

Diffuse parenchymal lung diseases (DPLDs) are a heterogeneous group of disorders characterized by varying degrees of inflammation and fibrosis involving the space between epithelial and endothelial basement membranes.

Among DPLDs of unknown aetiology one of the most commonly encountered is usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF), which carries the worst prognosis. In contrast, nonspecific interstitial pneumonia (NSIP), which belongs to the same DPLD group, has a more favourable prognosis. Based on the relative amount of inflammation and fibrosis observed on lung biopsies, at least two NSIP patterns have been suggested, namely cellular and fibrosing patterns. The long-term prognosis is excellent for patients with NSIP with a cellular pattern, as compared to patients with a fibrosing pattern.

We describe here a case of NSIP with a fibrosing pattern in a highly practiced runner showing an unexpectedly long-term favourable course, and consider the possible role of exercise in the diagnosis and clinical course of the disease.

The case that we describe reinforces the evidence that exercise training, that is a principal component of a pulmonary rehabilitation program, may have clinically significant effects on functional exercise capacity, especially if it is delivered early in the course of the disease.

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Key Words: Diffuse parenchymal lung diseases, non-specific interstitial pneumonia, exercise, pulmonary rehabilitation.

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Introduction

Diffuse parenchymal lung diseases (DPLDs) are a heterogeneous group of more than 200 separate disorders characterized by varying degrees of inflammation and fibrosis involving the space between epithelial and endothelial basement membranes (1) or, as occurs in a small number of diseases, by alveolar filling (1,2). Recently, DPLDs have been classified into four categories based on whether or not the cause is known (2).

The idiopathic interstitial pneumonias (IIPs) represent a subgroup of DPLDs of unknown aetiology. The American Thoracic Society/European Respiratory Society 2002 Consensus Classification Statement has subdivided IIPs into seven different clinical-radiologic-pathologic entities (3). Among the different types of IIPs one of the most commonly encountered is usual interstitial pneumonia/idiopathic pulmonary fibrosis (UIP/IPF), which carries the worst prognosis, with a median survival ranging from 2.5 to 3.5 years (4). In contrast, another type of IIP, namely nonspecific interstitial pneumonia (NSIP), has a more favourable prognosis (5). NSIP can be idiopathic or associated either to connective tissue diseases or environmental exposure. Based on the relative amount of inflammation and fibrosis observed on lung biopsies, at least two NSIP patterns have been suggested, namely cellular and fibrosing patterns (6). The long-term prognosis is excellent for patients with NSIP with a cellular pattern, as compared to patients with a fibrosing pattern,

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which mostly die within 5-10 years after diagnosis, the presence of honeycombing on high resolution computed tomography (HRCT) scan of the chest being a predictor of poor outcome (7).

We describe here a case of NSIP with a fibrosing pattern in a highly practiced runner showing an unexpectedly long-term favourable course, and consider the possible role of the exercise in the diagnosis and clinical course of the disease.

Case report

In July 2006, a 50year–old Caucasian man presented to us with non-productive cough and dyspnoea, which had recently started and were accentuated by exercise. He had no fever, chest pain, haemoptysis, loss of weight nor loss of appetite. He was a smoker of 35 pack-year and had a family history of COPD and high blood pressure. He worked as land surveyor and had an unremarkable past medical history. He was a highly practiced runner, whose exercise training program consisted of free running for 8 km in one hour, four 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 values of eritrosedimentation rate (ESR: 37 mm/h; normal value < 15), C-reactive protein (PCR: 13.7 mg/l, range 0-5), whereas rheumatoid factor, anti-nuclear antibodies, anti-neutrophilic cytoplasmic antibodies,

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double stranded DNA antibodies and extractable nuclear antigens were all in the normal range.

Pulmonary function were all in the normal range. They are showed in table 1. During a six-minute walk test the patient covered a distance of 663 metres, with a final Borg score of 1.5; no significant fall in arterial oxygen saturation was registered (table 2). A different result was obtained by a maximal cardiopulmonary exercise test that showed a significant fall in arterial oxygen partial pressure, from 81 to 69 mmHg (table 2).

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

Bronchoscopy was unremarkable. Analysis of the broncho-alveolar lavage fluid revealed no malignant cells, and a CD4/CD8 T-lymphocytes ratio of 0.9 (range 1.3-2.3). Microbiological examination of the bronchial washings was negative on both microscopy and culture for bacteria, fungi and mycobacteria. A right upper and lower lobe surgical lung biopsy specimen showed predominant features of NSIP, with a rather uniform fibrosing pattern, and associated lymphoid follicles, without fibroblastic foci.

On the basis of laboratory, histopathologic and radiologic results a diagnosis of NSIP fibrosing pattern was established.

Treatment with oral prednisone, at a dose of 1 mg/kg of body weight daily for twelve weeks was promptly initiated. Steroid dose was progressively tapered in the

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following six weeks and finally stopped. No relevant unwanted side effects from glucocorticosteroid treatment were recorded.

After the first few weeks of treatment the patient experienced a significant progressive improvement in both cough and exercise dyspnoea. Glucocorticosteroid treatment caused such an improvement that the patient was able not only to resume his exercise training, but also to reach in a few months almost the same intensity level of exercise adopted before the start of disease. A control HRCT scan carried out six months following the end of treatment was substantially unchanged and only demonstrated mild ground glass attenuation and patchy consolidation.

In December 2010, following four years of well-being, during which the usual exercise training was continued, the patient presented persisting cough, severe dyspnoea at rest and fever, so that he was urgently hospitalized. On admission laboratory blood tests showed a neutrophilic leucocytosis, and elevated ESR (56mm/h) and PCR (226 mg/dl). Pulmonary function tests revealed a spirometric pattern of moderate restrictive defect, a severe reduction in diffusion lung capacity for carbon monoxyde (DLCO), and a severe hypoxemia with metabolic alkalosis on blood gases analysis (table 1). A six-minute walk test showed a six minutes walk distance of 295 metres, with severe arterial oxygen desaturation from 89% to 81% (table 2).

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Doppler echocardiordiography demonstrated enlargement of the right atrium and ventricle, with a systolic right ventricular pressure of 45 mmHg, whereas left ventricular systolic and diastolic function was in the normal range.

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

An acute exacerbation of NSIP was diagnosed, and a treatment initiated with i.v. glucocorticosteroids (metilprednisolone, 5 mg/kg daily), i.v. antibiotics (an association of meropenem, voriconazole and levofloxacin), i.v diuretics, and oral N-acetylcysteine.

In two-week time the acute exacerbation receded, and the patient was assigned to a five-week pulmonary rehabilitation program, including respiratory muscles exercise training and upper and lower limb muscles training. Daily sessions included low-weight, high-repetition arm cycle ergometer training (30 minutes), treadmill walking (30 minutes), and bicycle training (30 minutes). Moreover, one hour educational class was performed three times a week. After rehabilitation, a consistent improvement in symptoms, lung function, and exercise tolerance was achieved (table 1), and the patient dismissed.

At the present time (December 2012), according to periodic telephone interviews, the patient is asymptomatic at rest, and is also able to continue regularly his

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exercise training practice (walking one hour a day, three times a week, with an oxygen supplementation of one litre/minute) although, as it could be expected, at a lower intensity level, in comparison to the level reached before the occurrence of the disease. Functional data are reported in table 1.

Discussion

NSIP, 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 IIPs (6).

Histopathologically, NSIP is characterized by a temporally uniform interstitial pneumonia, in contrast to the temporal heterogeneity observed in UIP (6, 8). Moreover, the fibroblast foci typically observed in UIP are rarely seen in NSIP (9).

On HRCT scan of the chest ground-glass opacities and reticular abnormalities with traction bronchiectasis are frequently seen and typically bilateral and symmetric, with lower lobe predominance, whereas honeycombing is generally absent and, even if present, is not the predominant radiographic abnormality (10).

The natural course of NSIP has not completely been elucidated (11), but, in general, patients demonstrate a significant response to glucorticosteroid treatment, with, in particular, the cellular pattern responding better than the fibrosing pattern (12). As a consequence, the prognosis of patients with a cellular pattern of NSIP is excellent

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(10), as compared to patients with NSIP with a fibrosing pattern, which present a 5-yr survival rate, substantially undistinguishable from patients with UIP (7).

The case reported here presents some peculiarities. First of all, it was probably the high degree of physical activity practiced by the patient that enabled us to make an early diagnosis of NSIP. In fact, exercise dyspnoea and cough, the typical symptoms of DPLDs, initially occurred in our patient exclusively in association with high intensity exercise, hence at a time well before they would probably have occurred if the patient had had a more sedentary life style.

The initial assessment of lung function showed no significant abnormalities compatible with the diagnosis of DPLD, except for a modest, non significant reduction in DLCO. In particular, the six-minute walk test was not able to document any significant oxyhaemoglobin desaturation in this stage of disease, probably because this test just reflects an exercise capacity sufficient for the usual activities of daily living. Instead, a maximal cardio-pulmonary exercise test was necessary in our well fitted patient to document an oxyhemoglobin desaturation suggestive of DPLD.

Following diagnosis and initial treatment with high dose oral glucocorticosteroids, the disease remained stable for four years, from 2006 until December 2010, when the patient experienced a severe exacerbation, with significant clinical, functional, and radiological worsening.

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Despite the favorable 5 year-survival rate of 74% of patients, it has been reported in one study that patients with a fibrosing NSIP are frequently hospitalized, and present a recurrence rate of 36% (13). In the same study 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 scans of the chest correlated well with serial changes of lung function, and the presence of honeycombing was strongly associated to poor prognosis (13). In the case reported here, despite the presence of radiological findings suggestive of poor prognosis (honeycombing and fibrosing pattern) the patient experienced a four year period of clinical stability. During this time, in spite of a progressive worsening of the chest HRCT scan, he was able to continue his high –level physical training program.

It should be recognized that several factors could have contributed to long term preservation of the performance status of the patient: a) an optimal baseline pulmonary function; b) a diagnosis made in a subclinical phase of the disease; c) a likely favourable influence given by the regular high level exercise activity performed by the patient during the course of the disease. With regard to the latter point, although exercise is generally recognized to have a role in the prevention and treatment of many chronic respiratory disorders (14, 15), in particular in COPD (16), the role of pulmonary rehabilitation in patients with DPLDs is less well defined. In

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fact, only low grade recommendations on exercise training for patients with DPLDs are provided in official guidelines for pulmonary rehabilitation (17, 18).

In contrast to these recommendations, evidence is now accumulating that pulmonary rehabilitation can result in clinically relevant improvements also in patients with DPLDs, although these improvements may vary greatly, depending on the diagnosis. IPF, for instance, seems to be less responsive to a pulmonary rehabilitation program in comparison to other DPLDs (19).

It might be postulated that physical deconditioning could have an unfavourable influence on the progression of DPLDs, as also happens in those chronic lung diseases that take advantage of pulmonary rehabilitation (16). With this regard, one point that should urgently be addressed is “when” pulmonary rehabilitation should be administered to these patients. The case we have described reinforces the evidence that pulmonary rehabilitation, more specifically exercise training, may have clinically significant effects on functional exercise capacity, especially if it is delivered early in the course of the disease.

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Table 1. Pulmonary function tests of the patient from baseline to the present.

	Baseline (year 2006)	Year 2010 (at admission)	Year 2010 (after-rehab)	Present (year 2012)
FVC	4.32 L (105% pred.)	2.77 L (68% pred.)	3.60 L (89% pred.)	3.44 L (81% pred.)
FEV1	3.43 L (101% pred.)	2.45 L (75% pred.)	2.97 L (92% pred.)	2.84 L (91% pred.)
FEV1/FVC%ratio	78	88	82	82
TLC	6.10 l (93% pred.)	3.56 l (54% pred.)	4.46 (68% pred.)	4.41 l (67% pred.)
DLCO/VA	4040 ml/min/mmHg (73% pred.)	1940 ml/min/mmHg (46% pred.)	2130 ml/min/mmHg (51% pred.)	2300 ml/min/mmHg (55% pred.)
PaO2	81 mmHg	51 mmHg	67 mmHg	68 mmHg

Abbreviations:
FVC = forced vital capacity
FEV1 = forced expiratory volume in one second
TLC = total lung capacity
DLCO/VA = diffusing capacity of lungs for CO/alveolar volume;
6MWD = six minute walk distance
PaO2 = arterial oxygen partial pressure

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Table 2. Exercise tests of the patient from baseline to the present.

	Baseline year 2006	Admission year 2010	Post-rehabilitation year 2010	Present year 2012
6 MWT				
Baseline SaO2	98%	98%	97%	97%
End SaO2	96%	88%	92%	90%
Distance	663 meters	295 meters	354 meters	383 meters
Final Borg score	1.5	7	2	3
CPET		ND	ND	ND
Vo2 peak	61% pred			
AT@VO2 max	57 (v.n.60-85)			
VO2/HR	63 pred			
Baseline PaO2	81 mmHg			
Final PaO2	69 mmHg			

6MWD = six minute walk distance
SaO2 = arterial oxygen saturation
CPET = cardiopulmonary exercise testing
VO2 peak = peak oxygen uptake
AT@VO2max= maximal oxygen uptake at anaerobic threshold
VO2/HR = oxygen uptake/heart rate
PaO2 = arterial oxygen partial pressure
ND = not determined