Interstitial lung disease as a presenting manifestation of microscopic polyangiitis successfully treated with mycophenolate mofetil

Sirs,

Microscopic polyangiitis (MPA) is a systemic necrotizing small-vessel vasculitis, without clinical or pathological evidence of necrotizing granulomatous inflammation, characterized mainly by pauci-immune segmental necrotizing glomerulonephritis and pulmonary capillaritis. Pulmonary involvement is seen in 25 to 55% of patients, with clinical features ranging from asymptomatic pulmonary infiltrates to hemoptysis, pleural effusion and pulmonary hemorrhage (1). Few cases had been reported with interstitial lung involvement in form of idiopathic pulmonary fibrosis (IPF) as presenting symptom of MPA (2-9).

A 61-year-old Caucasian woman was admitted to our hospital in February 1997 with a 6-year history of exerptional dyspnea without cough or hemoptysis. A presumptive diagnosis of interstitial lung disease was made on the basis of diffuse pulmonary interstitial infiltrates on chest x-ray, a severe restrictive pattern on pulmonary function tests (with a decreased diffusion lung capacity of carbon monoxide (DLCO) (56%) and a high resolution computed tomography (HRCT) scan who disclosed bibasilar interstitial infiltrates and extensive honeycombing images with peripheral distribution. Gasometry at baseline showed a moderate hipoxemia (PaO2 71 mm/Hg). Broncoscopy showed signs of chronic pneumopathy without luminal lesions on bronchial branches. Transbronchial biopsy was not performed. Serum creatinine and complement levels were normal and 24-hours proteinuria was 440 mg/dL. Antinuclear antibodies (ANA) were positive (1/160), while anti double-stranted deoxyribonucleic acid (DNA) antibodies, anti-neutrophil cytoplasmic antibodies (ANCA) and anti-glomerular basement membrane (GBM) antibodies were absent. She received treatment with oral prednisone (1mg/kg/day) with subsequent tapering for 1 year. In March 2000, Sjögren's syndrome (SS) was diagnosed based on xerophtalmia, xerostomia, a grade III salivary scintigraphy and positive Schirmer's test. At that time, ANA were positive (1/160), whilst anti Ro/SS-A and anti La/SS-B antibodies were negative. In July 2001, she was admitted for worsening of her dyspnea. Control HRCT scan disclosed persistent images of ground glass opacification and pulmonary function tests remained stable. Perinuclear (p)-ANCA were found to be positive with a titer of >1:160 and confirmed by ELISA myeloperoxidase (MPO) -ANCA (34 U/mL), anti GBM remained negative and 24-hr urine proteins were in the normal range (90 mg/dl). Pulse cyclophosphamide treatment (at 750 mg/m^2) was added (6 monthly and 5 every 3 months). Subsequently, she was on maintainance treatment with prednisone and azathioprine (2.5 mg *per os* daily and 50 mg *per os* daily respectively). In September 2002, she complained of distal paresthesias in lower limbs. A sensitive neuropathy was diagnosed by electromyography.

In June 2004, she was re-admitted due to malaise, weight loss, and worsening of her right lower limb paresthesias. Physical examination revealed a marked *livedo reticularis* over her thighs accompanied by malleolar edema. P-ANCA and proteinuria levels rose to 344 U/mL and 962 mg/dl, respectively. Urinary sediment revealed microhematuria. Percutaneous renal biopsy was performed showing necrotizing glomerulonephritis with focal extracapillary proliferation in 6 of 11 glomeuruli. Immunofluorescence was negative. MPA was diagnosed and mycophenolate mofetil (MMF) was started (1.5 g PO daily) with prednisone (1mg/kg/day in tapering doses) with an appropriate tolerance and without significant side effects. After 3-year follow-up, patient's clinical condition has remained stable, with neither renal relapses nor pulmonary symptoms. In April 2007, p-ANCA levels were 81 U/ml and 24-hrs proteinuria was 195 mg/dl.

To the best of our knowledge, there are only 12 previously well-documented cases of MPA with pulmonary fibrosis preceding the development of systemic features (mainly, renal involvement) of MPA. The clinical characteristics from these patients and the current case are collected in detail in Table I. Two aspects of the present case deserve special mention. First, the difficulties in achieving a definite diagnosis, mainly due to the long period between the onset of pulmonary symptoms and the overt renal involvement and ANCA positivity. The second aspect is the development of a marked proteinuria and the increase in ANCA levels in spite of a prolonged and sustained immunosuppressive treatment with cyclophosphamide, azathioprine, steroids, and finally, the satisfactory response to MMF. No prospective studies have been performed with MMF in MPA but case series indicate a response rate of 50-90% of those with active disease, and sustained remission rates of 50-90% (10).

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Competing interests: none declared.

Table I. Clinical characteristics of patients with MPA and IPF as a first manifestation.

Author (Ref)	Age/Gender	MPA clinical features	p-ANCA	Onset of IPF	Treatment	Outcome
1. Nada *et al*. (2)	74/F	Necrotizing GMN	+ ve	2 yrs before	S	Improvement
2. Nada *et al*. (2)	72/F	Fatigue, Necrotizing GMN small vessel pulmonary vasculitis	+ ve	2 yrs before	S	Partial response
3. Gaudin *et al*. (3)	33/F	AH, pulmonary capillaritis	+ ve	NR	NR	NR
4. Gaudin *et al*. (3)	8/M	AH, pulmonary capillaritis	+ ve	NR	NR	NR
5. Gaudin *et al*. (3)	12/M	AH, pulmonary capillaritis, BOOP	+ ve	NR	NR	NR
6. Becker-Merok *et al*. (4)	65/M	*Livedo reticularis*, arthritis weight loss, focal GMN peripheral neuropathy	80 U/mL	2 yrs before	S, Cyclo, AZA	Improvement
7. Hiromura *et al*. (5)	72/F	Fatigue, crescent GMN	1379 EU/mL	6 yrs before	S	Partial response
8. Mansi *et al*. (6)	55/F	Fever, arthralgias, crescent GMN	67 EU/mL	1 yr before	S, Cyclo	Improvement
9. Ortiz-Santamaría *et al*. (7)	83/F	Fever, small vessel vasculitis in muscular biopsy	1/1260	3 yrs before	S, Cyclo	Improvement
10. Eschun *et al*. (8)	67/F	Necrotizing GMN	1:16384	4 yrs before	S, Cyclo	Unsatisfactory
11. Eschun *et al*. (8)	64/M	Necrotizing GMN	1:128	4 yrs before	S, Cyclo	Unsatisfactory
12. Birnbaum *et al*. (9)	77/F	Vasculitic myopathy	23.5 IU/ml	6 mo before	S, Cyclo	Improvement
13. **Present case**	61/F	Peripheral neuropathy, *livedo reticularis*, weight loss, necrotizing GMN	344 U/ml	6 yrs before	S, Cyclo, AZA, MMF	Improvement

AH: alveolar hemorrhage; AZA: azathioprine; BOOP: bronchiolitis obliterans organizing pneumonia; Cyclo: cyclophosphamide; F: female; GMN: glomerulonephritis; IPF: idiopathic pulmonary fibrosis; M: male; MPA: microscopic polyangiitis; MMF: mycophenolate mofetil; Mo: months; NR: not reported; S: steroids.
*Eschun *et al*. described 4 more cases of MPA and IPF but presented simultaneously.

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Infliximab reduces oxidative stress in ankylosing spondylitis

Sirs,

Infliximab, a chimeric antibody to TNF-α, has been used effectively in rheumatoid arthritis. A recent study has shown that infliximab plays an important role as antioxidant in its therapeutic effect on rheumatoid arthritis (1).

The aim of this study was to determine the effect of infliximab on oxidative stress in patients with ankylosing spondylitis (AS). We studied 10 AS patients diagnosed according to the New York criteria for AS criteria (2); six of them presented an active disease (BASDAI >4, ESR >15 and CRP > 5 mg/L) and four were in inactive phase. All patients were under higher doses of non-steroidal anti-inflammatory drugs. These patients were compared with 8 healthy subjects matched by age and gender.

The subjects were included in the study after giving their informed consent. Active patients were treated with infliximab (5mg/kg/iv) at 0, 2 and 6 weeks, in accordance with ASAS recommendations (3). The effect of infliximab was determined after 6 weeks from the start of treatment and just before the third infusion. Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) were evaluated under basal conditions and 6 weeks after infliximab treatment. In addition, the following biochemical parameters that determine oxidative state were measured: plasma myeloperoxidase (MPO) concentration, lipid peroxidation (LPO), reduced glutathione (GSH), using reagents purchased from Oxis International (Portland, OR), *i.e*. MPO, LPO-586 and GSH-420 kits, respectively. Additionally, carbonylated protein (CP), glutathione peroxidase (GSH-Px), catalase (CAT) and superoxide dismutase (SOD) were evaluated by different methods (Levine *et al*. (4); Flohé and Gunzler (5); Aebi (6); and Sun *et al*. (7), respectively).

Statistical analysis (the Wilcoxon signed rank test, intragroup analysis; the Mann-Whitney U-test, intergroup analysis) showed a significant increase in ESR, CPR, and BASDAI in active AS (Table I), but were in the normal range in the control and inactive disease groups. Active AS also presented an intense oxidative stress compared with control and inactive groups characterized by significant increases in LPO, CP and MPO, whereas GSH, CAT, GSH-Px and SOD decreased significantly. The changes were reduced at 6 weeks after initial infliximab treatment.

The main findings in this preliminary study were that patients with active AS displayed intense oxidative stress with increased MPO concentration and that infliximab treatment reversed or counteracted the changes observed in AS active patients.

Recent studies (1) and other authors (8) have reported that infliximab treatment induced a significant decrease in oxidative stress markers in patients with active rheumatoid arthritis, establishing the beneficial effects of infliximab and the link between free radical protein damage and inflammation in rheumatoid arthritis. Various studies have also shown that reactive oxygen species play an important role in the pathogenesis of chronic inflammatory joint disease such as AS (9-11). However, only a few research studies have investigated the association between oxidative stress and AS. Moreover, according to our research, no studies have examined the relationship between oxidative stress in AS and infliximab effects.

Table I. Demographic and oxidative stress parameters of controls and all patients at baseline.

	Healthy subjects (Controls)	Ankylosing spondylitis (Patients)		
		Inactive	Active	
			Pre-treatment	Post-treatment
Number	8	4	6	
Sex (M/F)	3/5	3/1	4/2	
Age (yr)	38.7 ±11.26 (22-49)	35.33 ± 15.50 (24-53)	38.60 ± 9.50 (27-53)	
BASDAI		3 ± 1	6 ± 2	2 ± 1
ESR (mm/h)	12.29 ± 6.73	6.50 ± 4.95	27.50 ± 13.18*•	1.50 ± 0.7$
CRP (mg/L)	5.98 ± 8.6	2.00 ± 2.05	17.23 ± 14.38*•	1.20 ± 0.3$
WBC (x10^3/mL)	5.8 ± 1.8	5.5 ± 0.9	9.0 ± 0.9**••	5.6 ± 1.6$
MPO (ng/ml)	69.38 ± 1.92	81.44 ± 3.76**	109.94 ± 4.73***•	70.94 ± 4.89$$
LPO (nmol/dL)	65.3 ± 21.4	48.00 ± 26.7	345.6 ± 146.9*••	64.0 ± 19.0$
CP (nmol/dL)	10.2 ± 2.2	11.2 ± 4.3	21.4 ± 10.5*•	7.8 ± 1.5$
GSH (nmol/dL)	43.8 ± 3.9	39.1 ± 6.8	22.1 ± 6.2**•	38.4 ± 7.2
GSH-Px (U/dL)	13.6 ± 2.0	10.0 ± 1.4*	6.6 ± 1.8**•	11.9 ± 0.5$
CAT (U/dL)x100	11.1 ± 3.4	10.4 ± 0.6	5.6 ± 0.7*••	13.0 ± 1.1$
SOD (U/dL)	51.3 ± 5.7	39.8 ± 4.2*	28.4 ± 8.4**••	53.9 ± 10.0$

***p<0.001 *vs*. control group; **p<0.01 *vs*. control group; *p<0.05 *vs*. control group; •• p<0.01 *vs*. inactive group; •p<0.05 *vs*. inactive group; $$$p$<0.01 *vs*. pre-treatment; $ p<0.05 *vs*. pre-treatment.