Pulmonary fibrosis in patients with positive neutrophil cytoplasmic antibodies vasculitis

Sirs,

ANCA-positive vasculitis is a small-vessel systemic necrotising vasculitis (1). The most common presentation is pulmonary-renal syndrome, with necrotising glomerulonephritis and alveolar haemorrhage. In recent years, interstitial lung disease, often in the form of pulmonary fibrosis has been reported in patients with positive ANCA. Three patients with PF and ANCA-positive vasculitis are reported.

Case 1: A 72-year-old man, with a pulmonary fibrosis diagnosed by HRCT at age 69, was admitted for bilateral symmetrical polyarthritis, scapular and pelvic girdle syndrome, renal failure and haematuria. The immune study highlighted ANCA title of 1/320 with perinuclear pattern (anti-MPO >100 U/ml). Antinuclear antibodies (ANA), anti-GBM antibodies and rheumatoid factor (RF) were negative. A pauci-immune necrotising glomerulonephritis with a microscopic polyangiitis (MPA) was seen in the renal biopsy. He was treated with prednisone and cyclophosphamide with good response, then continued with azathioprine. The patient died of pneumonia after 3 years of the diagnosis of vasculitis.

Case 2: A 61-year-old man was admitted for simultaneous pulmonary fibrosis, palpable purpura, Raynaud's phenomenon and polyarthritis of the hands. The study highlighted a positive rheumatoid factor and cyclic citrullinated peptide (anti-CCP), ANCA titled by 1/640 cytoplasmic. Skin biopsy was consistent with leukocytoclastic vasculitis. The patient improved with low-dosage of glucocorticoids. Five years later differed multiple mononeuritis was found in a electromyogram. The muscle and nerve biopsy showed a small-medium vessel vasculitis. He started taking glucocorticoids and mycophenolic acid. The patient was exitus due to progression of lung disease after 6 years of diagnosis.

Case 3: A 71-year-old woman with a pulmonary fibrosis diagnosed 2 years before was admitted for polyarthritis of the hands and Raynaud's phenomenon. The immune study revealed ANA title of 1/160 with speckled and cytoplasmic pattern, ANCA title of 1/160 with perinuclear pattern, aMPO >100 U/ml and positive RF, anti-CCP antibodies was negative. She had progressive worsening of renal function with mild proteinuria. Renal biopsy was not conclusive. Treatment with oral corticosteroids and azathioprine was administered under the suspicion of possible ANCA-positive vasculitis but was finally discontinued due to liver toxicity. During follow-up, livedo reticularis was found in the lower extremities. A biopsy was performed and necrotising vasculitis of small and medium vessel was confirmed. Treatment with rituximab was initiated with good clinical evolution, remaining stable at present.

Pulmonary fibrosis is a rare clinical manifestation that has been associated with ANCA-positive vasculitis (2-6). Pulmonary fibrosis can appear before, concomitantly or after the diagnosis of vasculitis (7). Concurrent diagnosis is the most common presentation (2, 6, 8). The pathogenesis remains unclear, although different mechanisms have been proposed. One of them is the presence of repeated episodes of subclinical alveolar haemorrhage secondary to diffuse capillaritis (6-7). Another mechanism is related to the increased oxidative stress and proinflammatory response against neutrophil cytoplasmic antibodies, specifically the anti-myeloperoxidase antibodies (2, 5, 8). The fibrotic reaction would be the reparative response to lung damage caused by these mechanisms. Some authors have proposed to consider that the interstitial lung affectation as a limited form of microscopic polyangiitis (9).

In recent years around 131 clinical cases of pulmonary fibrosis and positive ANCA vasculitis have been published (3-4, 7). The average age of diagnosis of ANCA vasculitis is 68 years (10). The average age of our cases (Table I) is similar to those previously published.

Multiple studies observed that pulmonary fibrosis regards a worse prognosis with the presence of positive anti-MPO antibody (7). Survival at 5 years in patients with ANCA vasculitis is about 60% and is reduced to 29% when it is associated with pulmonary fibrosis (3). One of our patients died at six years of diagnosis of ANCA vasculitis because of progression of lung disease. Unlike previous studies described, he had no positive anti-MPO antibodies as a poor prognostic factor. The other patient also died as a result of pneumonia, while the third patient remains clinically stable.

In conclusion, we wanted to point out the importance of pulmonary fibrosis as a clinical manifestation of patients with ANCA-positive vasculitis, because it can help for the diagnosis and the treatment and may lead to improve the outcome of these patients.

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Table I. Main characteristics of patients.

Gender	Age (years)	Clinical manifestations	Pulmonary fibrosis	ANCA pattern	Anti-MPO	Diagnostic orientation	Treatment	Survival
M	72	Arthritis and renal involvement	Previous (3 years)	pANCA	Yes	MPA (renal biopsy)	CS+CYC, AZA	Death at 3 years
M	61	Arthritis, cutaneous involvement and peripheral neuropathy	Simultaneous	cANCA	No	ANCA-positive vasculitis (m/n biopsy)	CS+AZA, MMF	Death at 6 years
F	71	Arthritis, renal and cutaneous involvement	Previous (2 years)	pANCA	Yes	MPA (cutaneous biopsy)	CS+AZA, RTX	Clinical stability at 2 years

M: male; F: female; ANCA: anti-neutrophil cytoplasmic antibodies; MPA: microscopic polyangiitis; anti-MPO: anti-myeloperoxidase antibodies; CS: corticosteroids; CYC: cyclophosphamide; AZA: azathioprine; MMF: mycophenolate mofetil, m/n: muscle/nerve.