Case Report

Microscopic polyangiitis in a patient with preexistent pulmonary fibrosis by 8 years

Case report and review of the literature

Dimitrios Papadopoulos[1], Alexandra Nakou[2], Konstantinos Dalamarinis[3], Eleni Paraskevakou[4], Napoleon Karagianidis[5], Vasiliki Filaditaki[6]

[1]Resident doctor in pulmonology, 2nd Pulmonary Department, Sismanogleio General Hospital of Attiki, Marousi, Greece
[2]Pulmonologist, Junior Consultant, 2nd Pulmonary Department, Sismanogleio General Hospital of Attiki, Marousi, Greece
[3]Radiologist, Chief Physician, Department of Computed Tomography and Magnetic Resonance, Sismanogleio General Hospital of Attiki, Marousi, Greece
[4]Pathologist, Associate Professor, 1st Department of Pathology, Medical School, National and Kapodistrian University of Athens, Laiko General Hospital of Athens, Athens, Greece
[5]Pulmonologist, Chief Physician, 2nd Pulmonary Department, Sismanogleio General Hospital of Attiki, Marousi, Greece
[6]Pulmonologist, Head Physician, 2nd Pulmonary Department, Sismanogleio General Hospital of Attiki, Marousi, Greece

Key words:
- Microscopic Polyangiitis
- Pulmonary Fibrosis
- Antibodies
- Antineutrophil Cytoplasmic

Correspondence:
Vasiliki Filaditaki, Sismanogleio General Hospital of Attiki, 1 Sismanogliou street, 15126, Marousi, Greece, Tel.: 2132058424, fax: 2132058099, e-mail: bpnevmonologiki@sismanoglio.gr

ABSTRACT

Microscopic polyangiitis (MPA) is a systemic necrotising vasculitis that affects the small-caliber blood vessels and a common cause of pulmonary-renal syndrome. We present a patient case with manifestations of rapidly progressive glomerulonephritis and alveolar hemorrhage along with positive perinuclear antineutrophil cytoplasmic autoantibodies (p-ANCA) against myeloperoxidase (MPO). The patient was diagnosed with pulmonary fibrosis (PF) based on the findings of his chest computed tomography 8 years ago. 6 months ago he demonstrated nephrotic syndrome, had a kidney biopsy with findings of focal segmental necrotizing glomerulonephritis with glomerular crescents and in the presence of positive MPO-ANCA was diagnosed with MPA and treated with cyclophosphamide and prednisolone with partial response. In his present hospitalization he was admitted with symptoms of respiratory tract infection, which was successfully treated with antibiotics. Upon its remission he underwent a bronchoscopy with bronchoalveolar lavage, which was compatible with alveolar hemorrhage (50% hemosiderin-laden macrophages). The coexistence of MPA and PF is presenting more often in recent studies, as a result of the most widespread use of the high resolution chest computed tomography. The majority of these patients have positive MPO-ANCA, clinically manifested PF at the time of vasculitis diagnosis, radiological and pathological pattern of usual interstitial pneumonia (UIP) and a worse prognosis than those without PF. The pathogenetic association between these two conditions is not clear and 3 hypothetic mechanisms have been proposed: evolvement of fibrosis as a result of either the repeated episodes of alveolar hemorrhage or the induced oxidative stress in the presence of anti-MPO antibodies or reversely production of ANCA as a result of the fibrotic inflammatory process.

Pneumon 2016, 29(1):65-71.

INTRODUCTION

Microscopic polyangiitis (MPA) is a systemic necrotising vasculitis that affects the small-caliber blood vessels and a common cause of pulmonary-renal syndrome. Renal involvement is frequent and is characterized by focal necrotizing glomerulonephritis with absence of granulomas and no detection of immune deposits[1]. Pulmonary involvement can be seen in 25-55% of patients with diffuse alveolar hemorrhage being the prevailing manifestation[2].

In recent literature, pulmonary fibrosis is described more often as a lung manifestation of MPA. Its appearance may be concomitant with, occur after or predate by many years the diagnosis of MPA[3]. In the current report a patient case with PF preceding the vasculitis onset by 8 years is presented.

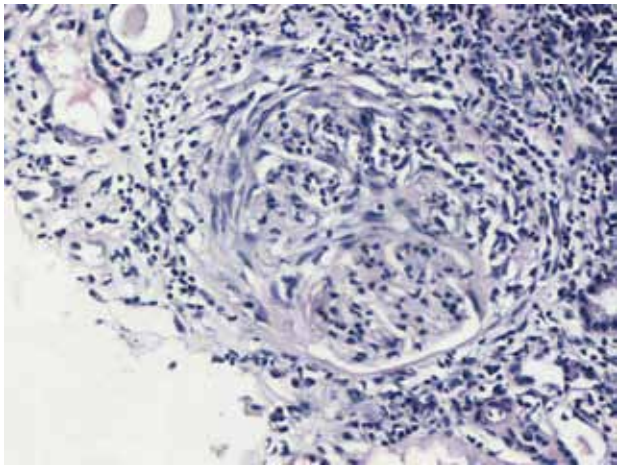

FIGURE 1. Kidney biopsy. Glomerulus with crescent (hematoxylin and eosin stain x40).

CASE REPORT

A 73-year-old man was admitted to our hospital in March 2015 with a two day history of fever and worsening of preexistent dyspnea. He was an ex-smoker (120 pack/year), former truck driver, had pulmonary fibrosis (PF) in his chest computed tomography since 2007 and only one prior hospitalization for respiratory symptoms a year ago. Due to his refusal of bronchoscopic evaluation, the etiology of PF was not investigated, nor a specific laboratory immunological screen performed, while there was no need for oxygen therapy. 6 months ago he was admitted to the nephrology department for investigation of nephrotic syndrome and underwent a kidney biopsy, which demonstrated focal segmental necrotizing glomerulonephritis with glomerular crescents (Figure 1). In combination with positive perinuclear antineutrophil cytoplasmic autoantibodies (p-ANCA) against myeloperoxidase (MPO) the diagnosis of MPA was set and he started treatment with prednisolone and cyclophosphamide (6 cycles intravenous per 3 weeks). Because of persistent proteinuria and positive ANCA after induction therapy, the patient entered into maintenance therapy with oral cyclophosphamide (150 mg daily) and prednisolone (30 mg daily).

Upon admission he had low grade fever, was hemodynamically stable and slightly tachypneic. His arterial blood gases showed chronic respiratory alkalosis (pO_2 71 mmHg, pCO_2 23 mmHg, pH 7.42, HCO_3 14.9 mmol/l). His physical examination revealed bilateral inspiratory fine crackles in the middle and lower zones, without clubbing or other manifestation from different systems. His laboratory tests demonstrated impaired renal function (Ur 150 mg/dl, Cre 2.5 mg/dl, without deviation from his baseline values), elevated inflammatory markers, hypoalbuminemia, microscopic hematuria and proteinuria, while his chest x-ray depicted bilateral reticular shadowing affecting the lower lung fields. He was diagnosed with pneumonia in the presence of immunosuppression and treated with ceftriaxone, linezolid, trimethoprim-sulfamethoxazole and oseltamivir (he had his flu vaccination only 4 days before admission), while he discontinued cyclophosphamide and continued with oral prednisolone in the same dose. His pulmonary function tests were compatible with a restrictive pattern with low diffusing capacity and little deviation from his last year test (Table 1). His blood, urine and sputum cultures for bacteria, fungi and mycobacteria were negative and so were the urine antigen for *Streptococcus pneumoniae* and *Legionella pneumophila* serotype 1 and the direct immunofluorescence in induced sputum for *Pneumocystis jiroveci*. His tuberculin skin test was also negative.

TABLE 1. Pulmonary function tests

	2014	2015
FVC ml (%)	2800 (67)	2670 (65)
FEV1 ml (%)	2390 (72)	2250 (69)
FEV1/FVC %	86	84
DLCO %	36	42

FVC: forced vital capacity, FEV1: forced expiratory volume in 1 second, DLCO: diffusing capacity for carbon monoxide

A chest high resolution computed tomography (HRCT) was obtained, where no consolidation was observed and interlobular septal thickening, traction bronchiectasis and honeycombing were recognized as in usual interstitial pneumonia (UIP) although with scattered distribution in all lung fields (Figure 2). With clinical improvement and restoration of inflammatory markers the patient underwent a bronchoscopy with bronchoalveolar lavage (BAL), the macroscopic appearance of which was not hemorrhagic although the cytological analysis revealed 50% hemosiderin-laden macrophages. BAL culture was negative for common pathogens, *Nocardia*, *Aspergillus* and mycobacteria, while infection by herpesviruses (*HSV, CMV, EBV, HHV6*) and atypical pathogens (*Pneumocystis jiroveci, Mycoplasma pneumoniae, Legionella pneumophila, Chlamydophila pneumoniae, Mycobacterium tuberculosis*) was not detected by PCR. For the purpose of differential diagnosis between infection and alveolar hemorrhage we repeated the bronchoscopy after a month, without significant change in BAL cytology.

The above findings suggest pulmonary involvement of MPA. Because of the patient's clinical stabilization no amendment was made to his previous treatment and he was referred to rheumatologic assessment.

DISCUSSION

MPA is defined according to the Chapel Hill classification as a systemic necrotizing vasculitis with few or no immune deposits affecting small vessels (capillaries, venules or arterioles), while involvement of medium arteries may also be present. It belongs to the category of ANCA-associated vasculitides (AAV), most commonly associated with a perinuclear pattern on immunofluorescence (p-ANCA) and specificity against MPO. The absence of granulomatous inflammation differentiates it from the other systemic vasculitides in its category, granulomatosis with polyangiitis (Wegener's) (GPA) and eosinophilic granulomatosis with polyangiitis (Churg-Strauss) (EGPA)[4]. The incidence of MPA in Europe ranges between 2.7 and 11.6 per million per year with a slight male predominance (1.8:1) and average age of onset between 50-60 years. Over 80% of patients experience renal involvement with rapidly progressive glomerulonephritis being the most common manifestation, pathologically characterized by focal segmental necrotizing glomerulonephritis with frequent presence of glomerular crescents. Pulmonary involvement can be seen in 25-55% of patients with diffuse alveolar hemorrhage caused by necrotic pulmonary

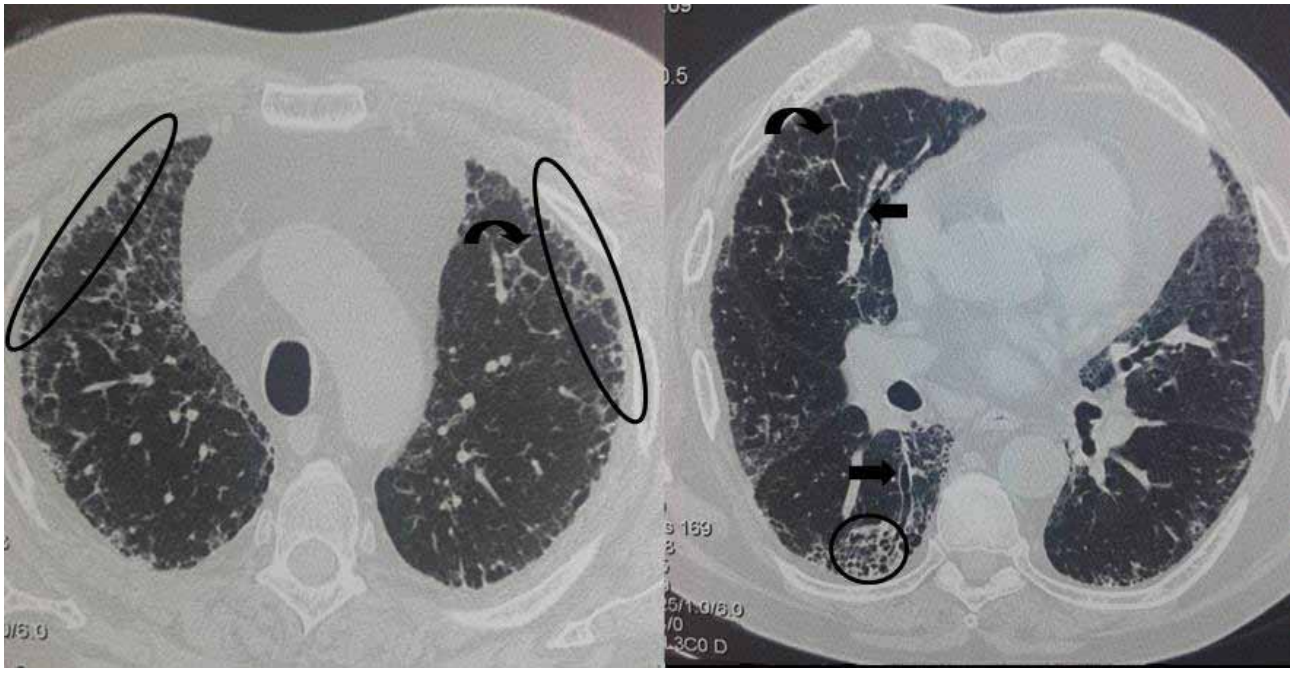

FIGURE 2. Chest HRCT. We recognized interlobular septal thickening (curved arrows), traction bronchiectasis (straight arrows) and honeycombing (ellipses).

capillaritis being the most common manifestation. Skin, musculoskeletal, gastrointestinal, neurological and ENT involvement is less common[2]. The presence of ANCA has 98% specificity for AAV and in case of MPA, MPO-ANCA are found in 60%, PR3-ANCA in 30% and no type in 10%. Clinical, in vivo and in vitro experimental data support a pathogenic role for ANCA in MPA via activation of neutrophils that express MPO or PR3 in their surface, adherence to the endothelium and production of reactive oxygen radicals[5].

Although a relative common finding in the course of connective tissue diseases, PF had been underestimated as a manifestation of AAV. Since 1990 when the first patient cases with coexistence of MPA and PF are described[6], the widespread use of HRCT has led to its frequent recognition and acceptance of the fact that it is not fortuitous because of their low prevalence, rather there is a pathogenetic association. In retrospective and perspective studies and trial databases from around the world[3, 7-17] the prevalence of PF in MPA patients ranges between 7.2% and 47.4%, with statistically significant higher percentages observed in Japanese series contrary to European ones[14], a finding that is probably associated with ethnic features or the varied accessibility to computed tomography, especially in subclinical or very mild cases[18]. There is also a statistically significant predominance of MPO-ANCA instead of PR3-ANCA in patients with PF and MPA in several studies. Characteristically, PF was clinically manifested at the time of MPA diagnosis in the overwhelming majority of patients, while at a rate between 14% and 68%, according to different studies, PF diagnosis preceded the development of MPA by months or years (Table 2). In idiopathic pulmonary fibrosis (IPF) patient cohorts (Table 3)[19-24] development of MPA has been observed in some patients with MPO-ANCA positivity at IPF diagnosis or with MPO-ANCA positive conversion during follow-up in a rate up to 41%, leading some authors to believe that patients with PF and MPO-ANCA positivity but without other manifestations of systemic vasculitis should be called "pulmonary limited vasculitis" as a phenotypic variant of MPA[25-27]. Predictive factors for MPO-ANCA positive conversion in these patients are rheumatoid factor positivity, elevated erythrocyte sedimentation rate, lower values of vital capacity and carbon monoxide diffusion capacity, higher percentage of eosinophils in BAL and frequency of pulmonary emphysema in computed tomography[23,24].

The most common radiological pattern in HRCT is the typical UIP pattern with reticular interlobular opacities, honeycombing, traction bronchiectasis and predominance in the subpleural regions of the lungs. In various histological specimens the UIP pattern is also predominant with characteristic absence of vasculitis in many cases[19,20,22,23], in contrary to AAV patient biopsies[28]. High incidence of histological findings, such as extensive interstitial fibrosis, lymphoid hyperplasia and bronchiolitis is observed in PF associated with collagen vascular diseases (CVD) instead of IPF[26]. In most studies, MPA patients with PF have a worse prognosis than those without PF[3,9,14-17], while prognosis in MPO-ANCA-positive PF is worse than in MPO-ANCA-negative PF associated with CVD but similar to IPF[19-21,23]. Among patients with MPO-ANCA-positive PF, the presence of high ANCA titers is also associated with worse prognosis[21,23].

There is no difference in treatment from the traditional MPA therapy and better results have been achieved in several studies with the combination of glucocorticoids with immunosuppressant agents (cyclophosphamide or rituximab) compared to glucocorticoids alone[10,11]. It has also been documented frequent administration of corticosteroids and immunosuppressants in IPF patients with positive MPO-ANCA than those with negative MPO-ANCA, without significant difference in median survival[23,24]. In a recent Japanese series, vital capacity improved >10% in approximately half of patients with pulmonary limited MPA when prednisolone was administered alone or in combination with another immunosuppressant agent[29]. More studies are required to ascertain if the benefit of this practice exceeds the cost of the treatment's adverse effects. However several authors recommend measuring and monitoring of MPO-ANCA titers in patients with initial IPF diagnosis in order to find those with increased likelihood for MPA development and put them under close monitoring so that they can benefit from faster diagnosis and treatment[3,6,8,15,20,21].

The pathogenetic mechanisms of PF in MPA remain poorly understood and 3 different hypotheses have been proposed. According to first, repeated episodes of alveolar hemorrhage, a common finding in active AAVs[30], leads to fibrosis in the same way as in idiopathic pulmonary hemosiderosis[31]. The second hypothesis is that MPO-ANCAs play a direct role in the pathogenesis of PF, through the oxidative stress that is produced by the interaction of MPO with circulating anti-MPO antibodies[32]. Third, the observation that PF is clinically manifested at the time of MPA diagnosis in the majority of patients has led to the hypothesis that IPF may induce MPA through the production of ANCA as a result of neutrophil destruction during the chronic inflammation process[23,33]. Tobacco smoke

TABLE 2. Features of MPA with PF patient series

Authors/ Year	Cases/Total (%)	Clasiffication n (%)	ANCA specificity n (%)	Time of PF diagnosis n (%)	HRCT pattern n (%)	Outcome n (%)
Hervier et al./2009[7]	12/517 AAV (2.3)	MPA 10 (83.3) GPA 2 (16.7)	MPO-ANCA 12 (100)	Concomitant 8 (66.7) Predating 3 (25) During follow-up 1 (8.3)	UIP 6 (50) NSIP 1 (8.3) Unspecified 5 (41.7)	Death 5 (41.7) Deterioration 2 (16.7) Stable 5 (41.7)
Tzelepis et al./2010[3]	13/33 (39.4)	MPA 13 (100)	p-ANCA 11 (84.6) p-ANCA+c-ANCA 1 (7.7) Negative 1 (7.7)	Concomitant 7 (53.8) Predating 5 (38.5) - median period 13 months During follow-up 1 (7.7)	UIP 7 (53.8) NSIP 4 (30.8)	Death 6 (46.2) Median survival 72 months
Arulkumaran et al./2011[8]	14/194 (7.2)	MPA 14 (100)	MPO-ANCA 14 (100)	Concomitant 9 (64.3) Predating 2 (14.3) During follow-up 3 (21.4)	UIP 8 (57.1) DIP 2 (14.3) NSIP 1 (7.1)	Death 10 (71.4) Mean survival 4.2 years
Keogh et al./2013[10]	68/-	MPA 68 (100)	p-ANCA 62 (91.2) c-ANCA 1 (1.5) Negative 5 (7.3)	Concomitant 45 (66.2) Predating 14 (20.6) During follow-up 9 (13.2)	UIP 68 (100)	Median survival: 138.2 months with CYC versus 51 months without CYC
Comarmond et al./2014[11]	49/-	MPA 40 (81.6) GPA 9 (18.4)	MPO-ANCA 43 (87.8) PR3-ANCA 2 (4.1) Unidentified 3 (6.1) Negative 1 (2)	Concomitant 21 (42.9) Predating 22 (44.9) During follow-up 6 (12.2)	Typical UIP 18 (36.7) Atypical UIP 6 (12.2) Fibrotic NSIP 3 (6.1) NSIP 4 (8.2) CPFE 9 (18.4) Indeterminate 2 (4.1)	Relapse 18 (36.7) End stage renal disease 4 (8.2) Chronic respiratory insufficiency 13 (26.5) Death 18 (36.7) 5-year survival rate 65.9%
Huang et al./2014[12]	19/67 (28.4)	MPA 19 (100)	MPO-ANCA 19 (100)	Concomitant 6 (31.6) Predating 13 (68.4) - mean period 9.5 months	UIP 19 (100)	Improvement 12 (63.2) Progression 1 (5.3) Death 6 (31.6)
Fernandez Casares et al./2015[15]	9/28 (32.1)	MPA 9 (100)	MPO-ANCA 9 (100)	Concomitant 4 (44.4) Predating 5 (55.6)	UIP 6 (66.7) Probable UIP 2 (22.2)	Death 4 (44.5) Deterioration 2 (22.2) Stable 3 (33.3)
Schirmer et al./2015[17]	22/144 (15.3)	MPA 22 (100)	-	Concomitant 17 (77.3) During follow-up 5 (22.7)	UIP 10/18 (55.6)	5-year survival rate 44%

UIP: usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, DIP: desquamative interstitial pneumonia, CPFE: combined pulmonary fibrosis and emphysema, CYC: cyclophosphamide

exposure may play an initiating role in this process by stimulating MPO expression in airway epithelial cells and inducing infiltration of neutrophils in lung structures[20].

CONCLUSION

From this case and the following literature review we conclude that: a) PF may precede the development of

TABLE 3. Features of IPF with positive MPO-ANCA patient series

Authors/Year	Cases/Total (%)	ANCA specificity n (%)	Time of ANCA positivity n (%)	HRCT pattern n (%)	Vasculitis diagnosis n (%)	Outcome n (%)
Homma et al./2004[19]	31/247 IPF+CTD (12.6)	MPO-ANCA 31 (100)	Concomitant 31 (100)	Honeycombing 26 (83.9)	MPA 8 (25.8) CTD 14 (45,2)	Death 13 (41.9) 5-year survival rate 50%
Foulon et al./2008[20]	17/-	MPO -ANCA 6 (35.3) PR3-ANCA 1 (5.9) Lf-ANCA 1 (5.9) HNE-ANCA 1 (5.9) Unidentified 8 (47)	Concomitant 3 (17.6) During follow-up 14 (82.4)	Honeycombing 17 (100)	MPA 7 (41.2) - mean period 53 months	Death 10 (58.8) - MPA 6 (85.7) 5-year survival rate 60%
Nozu et al./2009[21]	19/53 (35.8)	MPO-ANCA 17 (89.5) PR3-ANCA 2 (10.5)	Concomitant 19 (100)	Honeycombing 11/15 (73.3)	MPA 4 (21.1) - mean period 17 months	Death 6 (31.6) - MPA 2 (50) 5-year survival rate 60%
Tanaka et al./2012[22]	9/224 (4)	MPO-ANCA 9 (100)	Concomitant 9 (100)	UIP 6 (66.7) NSIP 1 (11.1) OP 1 (11.1) DAD 1 (11.1)	MPA 0 (0)	Death 4 (44.4) Median survival 46 months
Ando et al./2013[23]	9/61 (14.8)	MPO-ANCA 9 (100)	Concomitant 3 (33.3) During follow-up 6 (66.7) - median period 23 months	Honeycombing 9 (100)	MPA 2 (22.2) UCTD 3 (33.3)	Death 6 (66.7) - MPA 2 (100) Median survival 62 months
Kagiyama et al./2015[24]	65/300 (21.7)	MPO-ANCA 35 (53.8) PR3-ANCA 30 (46.2)	Concomitant 36 (55.4) During follow-up 29 (44.6)	-	MPA 9 (13.8)- mean period 4.3 years	5-year mortality rate 61.3%

CTD: connective tissue disease, Lf: lactoferrin, HNE: human neutrophil elastase, UIP: usual interstitial pneumonia, NSIP: nonspecific interstitial pneumonia, OP: organizing pneumonia, DAD: diffuse alveolar damage, UCTD: undifferentiated connective tissue disease

MPA by many years, with a mostly unclear pathogenetic mechanism, b) monitoring of ANCA titers is important in finding those patients that should undergo a more systematic screening for early detect of renal involvement, c) BAL can be useful in discovery of subclinical alveolar hemorrhage and should be performed in patients with PF and positive ANCA and d) the decision for initiation of immunosuppressant therapy in cases of pulmonary limited MPA should be made individualized, since it is not documented by large prospective studies and is associated with serious adverse effects, with infections being the most dominant of them.

REFERENCES

1. Guillevin L, Durand-Gasselin B, Cevallos R, et al. Microscopic polyangiitis: clinical and laboratory findings in eighty-five patients. Arthritis Rheum 1999; 42:421-30.
2. Chung SA, Seo P. Microscopic polyangiitis. Rheum Dis Clin North Am 2010; 36:545–58.
3. Tzelepis GE, Kokosi M, Tzioufas A, et al. Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. Eur Respir J 2010; 36:116-21.
4. Jennette JC, Falk RJ, Bacon PA, et al. 2012 revised International Chapel Hill Consensus Conference Nomenclature of Vasculitides. Arthritis Rheum 2013; 65:1-11.
5. Kallenberg CG, Heeringa P, Stegeman CA. Mechanisms of Disease: pathogenesis and treatment of ANCA-associated vasculitides.

Nat Clin Pract Rheumatol 2006; 2:661-70.
6. Nada AK, Torres VE, Ryu JH, Lie JT, Holley KE. Pulmonary fibrosis as an unusual clinical manifestation of a pulmonary-renal vasculitis in elderly patients. Mayo Clin Proc 1990; 65:847-56.
7. Hervier B, Pagnoux C, Agard C, et al. for the French Vasculitis Study Group. Pulmonary fibrosis associated with ANCA-positive vasculitides. Retrospective study of 12 cases and review of the literature. Ann Rheum Dis 2009; 68:404-7.
8. Arulkumaran N, Periselneris N, Gaskin G, et al. Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study. Rheumatology (Oxford) 2011;50:2035-43.
9. Ahn JK, Hwang JW, Lee J, Jeon CH, Cha HS, Koh EM. Clinical features and outcome of microscopic polyangiitis under a new consensus algorithm of ANCA-associated vasculitides in Korea. Rheumatol Int 2012; 32:2979-86.
10. Keogh K, Baqir M, Specks U, et al. Microscopic polyangiitis in the setting of usual interstitial pneumonia. Presse Med 2013; 42:703.
11. Comarmond C, Crestani B, Tazi A, et al. Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. Medicine (Baltimore) 2014; 93:340-9.
12. Huang H, Wang YX, Jiang CG et al. A retrospective study of microscopic polyangiitis patients presenting with pulmonary fibrosis in China. BMC Pulm Med 2014; 14:8.
13. Sada KE, Yamamura M, Harigai M, et al. Classification and characteristics of Japanese patients with antineutrophil cytoplasmic antibody-associated vasculitis in a nationwide, prospective, inception cohort study. Arthritis Res Ter 2014; 16:R101.
14. Furuta S, Chaudhry AN, Hamano Y, et al. Comparison of phenotype and outcome in microscopic polyangiitis between Europe and Japan. J Rheumatol 2014; 41:325-33.
15. Fernandez Casares M, Gonzalez A, Fielli M, Caputo F, Bottinelli Y, Zamboni M. Microscopic polyangiitis associated with pulmonary fibrosis. Clin Rheumatol 2015; 34:1273-7.
16. Hirayama K, Kobayashi M, Usui J, et al. on behalf of the Japanese RPGN Study Group of Progressive Renal Disease. Pulmonary involvements of anti-neutrophil cytoplasmic autoantibody-associated renal vasculitis in Japan. Nephrol Dial Transplant 2015; 30 Suppl 1:i83-93
17. Schirmer JH, Wright MN, Vonthein R, et al. Clinical presentation and long-term outcome of 144 patients with microscopic polyangiitis in a monocentric German cohort. Rheumatology (Oxford) 2015; pii:kev286.
18. Katsumata Y, Kawaguchi Y, Yamanaka H. Interstitial Lung Disease with ANCA-associated Vasculitis. Clin Med Insights Circ Respir Pulm Med 2015; 9(Suppl 1):51-6.
19. Homma S, Matsushita H, Nakata K. Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides. Respirology 2004; 9:190-6.
20. Foulon G, Delaval P, Valeyre D, et al. ANCA-associated lung fibrosis: analysis of 17 patients. Respir Med 2008; 102: 1392-8.
21. Nozu T, Kondo M, Suzuki K, Tamaoki J, Nagai A. A comparison of the clinical features of ANCA-positive and ANCA-negative idiopathic pulmonary fibrosis patients. Respiration 2009; 77:407-15.
22. Tanaka T, Otani K, Egashira R, et al. Interstitial pneumonia associated with MPO-ANCA: clinicopathological features of nine patients. Respir Med 2012; 106:1765-70.
23. Ando M, Miyazaki E, Ishii T, et al. Incidence of myeloperoxidase anti-neutrophil cytoplasmic antibody positivity and microscopic polyangitis in the course of idiopathic pulmonary fibrosis. Respir Med 2013; 107:608-15.
24. Kagiyama N, Takayanagi N, Kanauchi T, et al. Antineutrophil cytoplasmic antibody-positive conversion and microscopic polyangiitis development in patients with idiopathic pulmonary fibrosis. BMJ Open Resp Res 2015; 2:e000058.
25. Ozaki S, Atsumi T, Hayashi T, et al. Severity-based treatment for Japanese patients with MPO-ANCA-associated vasculitis: the JMAAV study. Mod Rheumatol 2012; 22:394-404.
26. Homma S, Suzuki A, Sato K. Pulmonary involvement in ANCA-associated vasculitis from the view of the pulmonologist. Clin Exp Nephrol 2013; 17:667-71
27. Flores-Suárez LF. Limited pulmonary MPA, a new MPA entity? A rheumatologist's perspective. Clin Exp Nephrol 2013; 17:672-5.
28. Gaudin PB, Askin FB, Falk RJ, Jennette JC. The pathologic spectrum of pulmonary lesions in patients with anti-neutrophil cytoplasmic autoantibodies specific for anti-proteinase 3 and anti-myeloperoxidase. Am J Clin Pathol 1995; 104:7-16.
29. Yamada H. ANCA-associated lung fibrosis. Semin Respir Crit Care Med 2011; 32:322-7.
30. Schnabel A, Reuter M, Csernok E, Richter C, Gross WL. Subclinical alveolar bleeding in pulmonary vasculitides: correlation with indices of disease activity. Eur Respir J 1999; 14:118-24.
31. Birnbaum J, Danoff S, Askin FB, Stone JH. Microscopic polyangiitis presenting as a "pulmonary-muscle" syndrome: is subclinical alveolar hemorrhage the mechanism of pulmonary fibrosis? Arthritis Rheum 2007; 56:2065-71.
32. Guilpain P, Chereau C, Goulvestre C, et al. The oxidation induced by antimyeloperoxidase antibodies triggers fibrosis in microscopic polyangiitis. Eur Respir J 2011; 37:1503-13.
33. Ando Y, Okada F, Matsumoto S, Mori H. Thoracic manifestation of myeloperoxidase-antineutrophil cytoplasmic antibody (MPO-ANCA)-related disease. CT findings in 51 patients. J Comput Assist Tomogr 2004; 28:710-6.