ANCA-Associated Lung Fibrosis

Hidehiro Yamada, M.D.[1]

ABSTRACT

The possible link between pulmonary fibrosis, anti-neutrophil cytoplasmic autoantibody (ANCA) positivity, and vasculitis is poorly understood. During the past 6 years, five retrospective case-control studies have been published. These studies suggest that pulmonary fibrosis (PF) is an underestimated manifestation of ANCA-associated vasculitis. Common clinical characteristics include older age (around 70 years), constant positivity of myeloperoxidase (MPO)-ANCA and the poor prognosis of the pulmonary disease. The diagnosis of PF often predates the development of vasculitis. There are no significant differences of pulmonary function parameters, bronchoalveolar lavage analysis, or high-resolution computed tomographic (HRCT) findings between ANCA-associated PF and idiopathic pulmonary fibrosis (IPF). The high mortality rate of ANCA-associated PF indicates that a search for ANCAs should be performed at diagnosis in every patient with PF because the presence of ANCAs increases the risk of development of vasculitis and should promote specific monitoring of patients with positive MPO-ANCA.

KEYWORDS: MPO-ANCA, pulmonary fibrosis, interstitial lung disease, microscopic polyangiitis

In 1990, Nada et al[1] reported the first three patients who had an initial diagnosis of idiopathic pulmonary fibrosis (IPF) but later were correctly diagnosed as having pulmonary-renal vasculitis. Circulating perinuclear-antineutrophil cytoplasmic autoantibodies (P-ANCAs) were detected in two patients. These seminal cases underscored the importance of a high index of suspicion for systemic vasculitis in elderly patients and the need to consider vasculitis in the differential diagnosis of IPF. Since then, several small series described patients with pulmonary fibrosis (PF) associated with ANCA-positive vasculitis [e.g., microscopic polyangiitis (MPA) and rapidly progressive glomerulonephritis]. Further, PF has been observed in pathological series of ANCA-associated lung diseases.[2,3] However, the possible link between PF, ANCA positivity, and vasculitis is poorly understood.

During the past 6 years, five retrospective case-control studies were published[4–8] (Table 1). These studies indicate that PF is an underestimated manifestation of ANCA-associated vasculitis.

CLINICAL CHARACTERISTICS OF ANCA-ASSOCIATED LUNG FIBROSIS

Hervier et al[6] retrospectively investigated 12 patients with PF fulfilling the international consensus statement criteria for IPF[9] and associated with ANCA-positive vasculitis (fulfilling the Chapel Hill Classification criteria for vasculitis).[10] Common clinical characteristics

[1]Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, Miyamaeku, Kawasaki, Japan.

Address for correspondence and reprint requests: Hidehiro Yamada, M.D., Division of Rheumatology and Allergy, Department of Internal Medicine, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamaeku, Kawasaki 216-8511, Japan (e-mail: guriko@marianna-u.ac.jp).

Lung Vasculitis and Alveolar Hemorrhage; Guest Editor, Loïc Guillevin, M.D.

Semin Respir Crit Care Med 2011;32:322–327.
DOI: http://dx.doi.org/10.1055/s-0031-1279828.
ISSN 1069-3424.

Table 1 Review of the Case-Control Studies on ANCA-Associated Pulmonary

First Author Year	Subject	No. (M:F)	Age (Range)	Smoker	ANCA Specificity	CT Pattern	%FVC Mean	DLco% Mean	Concurrent Vasculitis	Vasculitis after PF	Chronology PF to ANCA-V	Outcome	Control	Comparison
Homma 2004[4]	MPO-ANCA-positive PF	31 (17:14)	69 (45–87)	16/31 (52%)	All MPO	Honeycomb 26/31 (84%)	85.2	nd	MPA: 8 (23%) CTD:14 none:9	nd	nd	survival: 50% at 5-year	126 IPF 64 CTD 26 RA	survival: similar to IPF & RA worse than CTD
Foulon 2008[7]	ANCA-positive PF	17 (14:3)	66 (45~84)	11/17 (65%)	14 p-ANCA 6 MPO 1 PR3 10 others	Honeycomb 100%	82.1	49.4	MPA: 1 (6%)	MPA: 6 (35%)	53 months (15–137)	survival: 60% at 5-year	12 ANCA -negative PF	Similar Characteristics & survival
Hervier 2009[6]	PF in ANCA-V	12 (9:3)	70.7 (64–78)	8/12 (67%)	All MPO	UIP: 6 NSIP: 1 ND: 5	75	60.5	MPA: 6 (67%) WG: 2 (17%)	MPA: 3 (25%)	Several years	PF progressed: 5/12	17 cases Previously reported	Similar Clinical features
Nozu 2009[5]	ANCA-positive PF	19 (7:12)	69 (52–80)	9/19 (47%)	17 MPO 2 PR3	Honeycomb 11/15 (73%)	86.0	41.4	MPA: 4 (21%)	nd	nd	PF improved: 14/19 survival: 60% at 5-year	34 ANCA -negative PF	Similar survival
Tzelepis 2010[8]	PF in MPA	13 (9:4)	57	nd	All p-ANCA	UIP: 7 NSIP: 4 ND: 2	75.4	55.5	MPA: 12 (36%)	MPA: 7 (54%)	13 months (5–120)	survival: 60% at 5-year 4 died of PF	20 MPA Without PF	poorer survival

ANCA-V, ANCA-associated systemic vasculitis; CTD, connective tissue diseases; IPF, idiopathic pulmonary fibrosis; MPA, microscopic polyangiitis; MPO, myeloperoxidase; nd, not described; ND, not determined; NSIP, nonspecific interstitial pneumonia; PR3, proteinase 3; RA, rheumatoid arthritis; UIP, usual interstitial pneumonia; WG, Wegener granulomatosis.

included older age (around 70 years) at diagnosis of ANCA-associated vasculitis, constant presence of MPO-ANCA, and the poor prognosis of the pulmonary disease. Subsequent case-control studies (see Table 1) demonstrated additional characteristics. There is a tendency for a male predominance. Foulon et al[7] and Nozu et al[5] compared clinical characteristics between ANCA-positive and ANCA-negative PF patients. Both studies found no significant differences in pulmonary functional parameters at diagnosis, bronchoalveolar lavage cytological analysis, or high-resolution computed tomographic (HRCT) findings.

CLINICAL COURSE OF ANCA-ASSOCIATED LUNG FIBROSIS

Data regarding the relative timing of fibrosis diagnosis, ANCA positivity detection, and vasculitis occurrence are limited. The diagnosis of PF often predates the development of vasculitis. However, ANCA is usually measured at the diagnosis of vasculitis, not at PF diagnosis. Foulon et al[7] compared the clinical presentation of patients with ANCA-positive PF with a control group of ANCA-negative PF (Table 1). Microscopic polyangiitis (MPA) was diagnosed in 7/17 patients (41%) in the ANCA-positive cohort and was never observed in 12 ANCA-negative patients. In six of seven patients, MPA developed after PF, with a mean delay of 53 months (range: 15 to 137 months) (Table 1). The diagnosis of PF and MPA was concomitant in only one patient. Among seven patients with MPA, alveolar hemorrhage was noted in six. During follow-up, 10/17 patients in the ANCA-positive cohort died (three directly related to vasculitis). Tzelepis et al[8] reported 33 patients with MPA and (positive) ANCA. PF was present in 12 (36%) at presentation and developed in one additional patient while on therapy for MPA. All had renal involvement (necrotizing, segmental glomerulonephritis). Prognosis was worse among patients with PF (six deaths in the PF cohort compared with one death in the non-PF cohort, $p = 0.02$). Nozu et al retrospectively reviewed 53 patients with PF who had been tested for ANCA.[5] Overall, circulating ANCAs were found in 19 (37%) [including MPO in 17 and proteinase 3 (PR3) in two]. Among patients with ANCA-positive PF, patients with MPA had higher ANCA titer than those without vasculitis.[5] It remains unclear, however, whether high ANCA titers can predict the development of vasculitis among patients with ANCA-positive PF.

Outcome

Prognosis of ANCA-associated PF is generally poor. In the retrospective study by Nozu et al, survival was analyzed among 53 patients with IPF.[5] Among 19 patients with ANCA-positive PF, six (31%) died (1 to 90 months) and four (21%) were lost to follow-up. Among 34 patients in the ANCA-negative cohort, 15 died (44%) (1 to 58 months) and 12 (36%) were lost to follow-up. These mortality rates were not statistically different between cohorts. However, the low-titer (<50 EU) group showed better survival than the high-titer (>50 EU) group in ANCA-positive lung fibrosis. In this retrospective study, HRCT improved with corticosteroid/immunosuppressive therapy in 14/17 patients with ANCA-positive PF.[5] However, details of extent of improvement were not provided.

Foulon et al studied 17 patients with ANCA-associated PF.[7] During the course of follow-up, seven patients developed MPA. Six of 7 patients with MPA died (three as a direct result of vasculitis).[7] In addition, four of the 10 patients who did not develop MPA died during follow-up. Acute respiratory failure due to an exacerbation of PF occurred in two patients (BAL in one patient at the time of exacerbation showed no alveolar hemorrhage). Hervier et al retrospectively assessed 12 patients with PF and (positive) ANCA (all MPO-ANCA).[6] Two died during induction therapy (within 7 months) for vasculitis. Three died of progressive respiratory failure (range 37 to 67 months). In the remaining patients, the disease worsened in two and stabilized in five. Homma et al retrospectively reviewed 31 patients with PF and (positive) MPO-ANCA; [including 22 with connective tissue disease (CTD) and nine of unknown etiology].[4] Overall, 13/31 (24%) died; causes of death included worsening PF ($n = 5$), pneumonia ($n = 4$), lung cancer ($n = 2$), and gastrointestinal bleeding ($n = 2$).

The prognosis of ANCA-associated PF is variable. Chronic forms of lung fibrosis with predominant honeycombing will likely not respond to immunosuppressive therapy (Fig. 1), whereas subacute disease (particularly when ground-glass opacities (GGOs) are present on HRCT) may respond to immunosuppressive therapy[11] (Fig. 2).

The high mortality rate of ANCA-associated PF suggests that a search for ANCAs should be performed at diagnosis in every patient with PF because the presence of ANCAs will increase the risk of development of a vasculitis and promote specific monitoring, especially if the ANCAs are the MPO epitope.

Pathology

Reports on the histopathology of ANCA-associated PF are limited. Gaudin et al[2] reviewed the histological features of lung diseases in 27 patients (positive) for either cytoplasmic-ANCA (c-ANCA) ($n = 13$) or MPO-ANCA ($n = 14$). Predominant findings included capillaritis (17 patients, 63%), interstitial lesions (20 patients, 74%); necrotizing granulomatous inflammation (eight patients, 30%), fibrosis (13 patients, 48%), and chronic inflammation (12 patients, 44%). Homma et al[4]

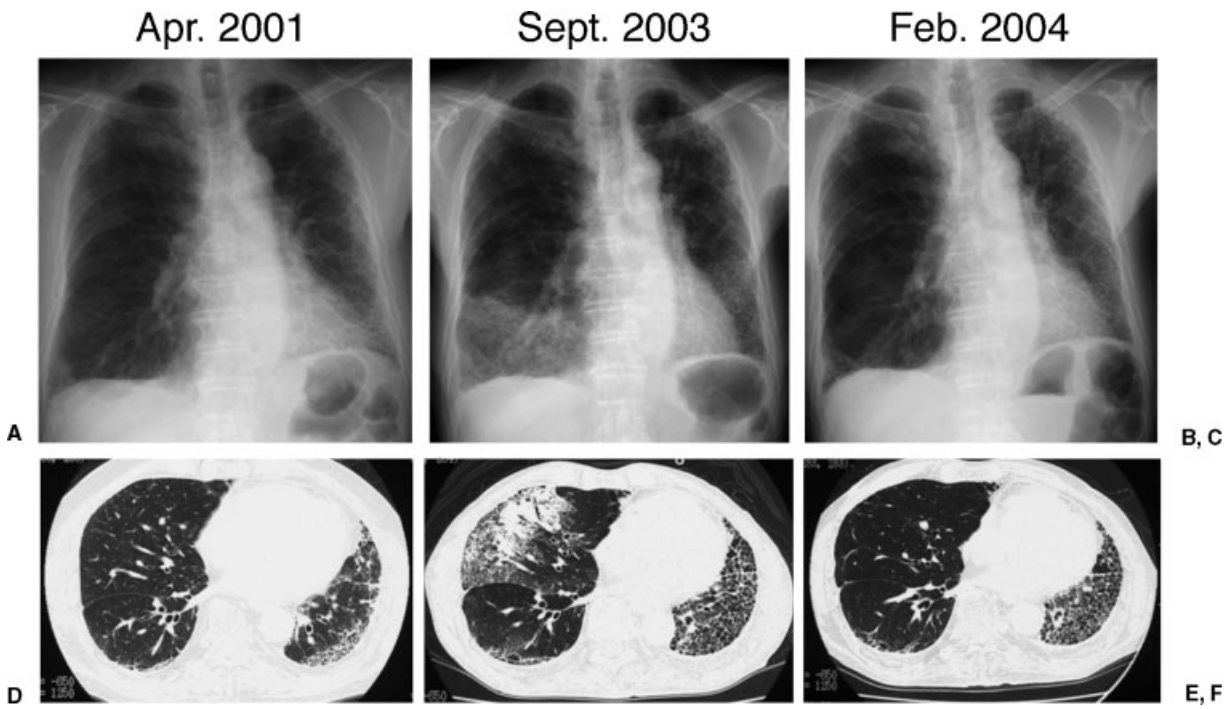

Figure 1 Chronic form of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated lung fibrosis during the course of vasculitis. (A, D) A 71-year-old man presented to the hospital because of dry cough in April 2001. He had a 2-year history of idiopathic pulmonary fibrosis diagnosed at the local hospital. High-resolution computed tomography showed a usual interstitial pneumonia pattern and was followed without any treatment. (B, E) He was admitted to the hospital in September 2003 because of hemoptysis and dyspnea. At the time of admission, hematuria, anemia, renal failure (serum creatinine 3.0 mg/dL), and elevated myeloperoxidase ANCAs (429 EU) were evident. Renal biopsy demonstrated crescentic glomerulonephritis. He was diagnosed to have microscopic polyangiitis with alveolar hemorrhage and renal involvement. Treatment with monthly IV cyclophosphamide and prednisolone resulted in clinical remission. (C, F) Pulmonary fibrosis did not progress and remained relapse free for >5 years.

retrospectively studied a cohort of 31 patients with PF who also had MPO-ANCAs. They identified eight patients with MPA. Of 15 biopsy and postmortem specimens available for histopathological study, 11 had background features of usual interstitial pneumonia (UIP) pattern. Five specimens showed vasculitis in pulmonary and/or bronchial arterioles. In addition, lymphoid hyperplasia and organizing pneumonia were often observed, similar to PF complicating CTD. Birnbaum et al[11] reported a patient with MPA who had subacute progression of interstitial lung disease and muscle involvement. Review of the lung biopsy specimen after the diagnosis of MPA revealed some findings suggestive of UIP, including foci of fibroblast proliferation, architectural remodeling with a honeycomb pattern, and a spatially and temporally heterogeneous pattern of fibrosis. In addition, there were histopathological features inconsistent with UIP such as foci of leukocytoclastic capillaritis, constrictive bronchiolitis, and a chronic hemorrhagic component, with regions of hemosiderin-laden macrophages juxtaposed with fibroblast foci. French investigators reported three ANCA-positive patients who had undergone surgical lung biopsy; all cases showed UIP pattern with no vasculitis.[7] These discrepant results may be partly explained by the temporal and spacial heterogeneity of ANCA-associated PF. Eschun et al described histological findings (from surgical lung biopsy) in a patient with MPA who presented with PF.[12] Wedge resection from the upper lobe revealed focal alveolar hemorrhage and nonspecific interstitial pneumonitis (NSIP) without significant fibrosis or honeycombing; however, specimens obtained from the lower lobe demonstrated honeycombing. HRCT may be a surrogate marker for fibrosis or alveolitis. UIP pattern is most common on computed tomography (CT), but CT features are heterogeneous[5–8] (Table 1). In two small series, GGOs were noted in 100%[7] and 80%[5] of cases, respectively, in addition to the typical UIP features such as honeycombing and traction bronchoectasis (Table 1).

Hypothetical View on the Pathogenesis of ANCA-Associated Lung Fibrosis

At least two mechanisms have been proposed for the development of ANCA-associated PF. The first hypothesis is that recurrent, subclinical alveolar hemorrhage might contribute to the development of PF in ANCA-associated vasculitis. This hypothesis is supported by

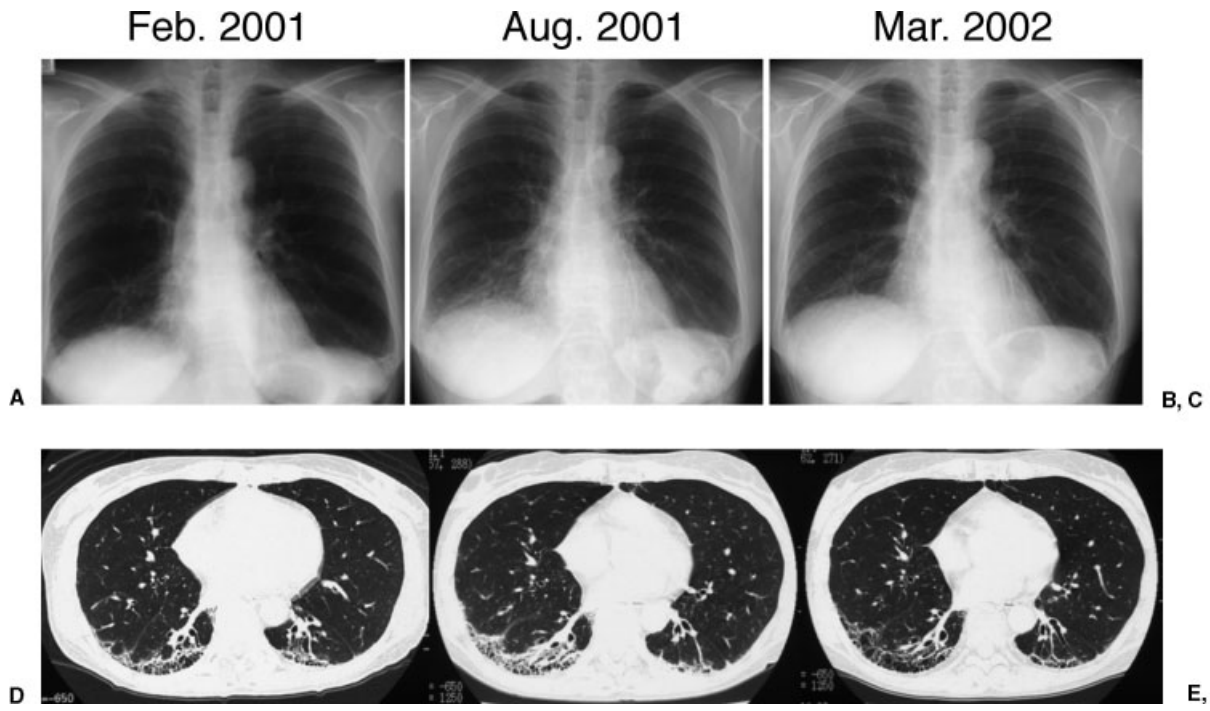

Figure 2 Subacute form of anti-neutrophil cytoplasmic autoantibody (ANCA)-associated lung fibrosis. A 59-year-old female was admitted to the hospital in August 2001 because of increasing cough and dyspnea. (A, D) One year before admission, she was diagnosed with interstitial lung disease, but no treatment was advised. (B, E) On admission she was febrile with episcleritis and mononeuritis multiplex. Chest x-ray and high-resolution computed tomography revealed worsening of interstitial lung disease. Renal biopsy showed crescentic necrotizing glomerulonephritis. myeloperoxidase (MPO)-ANCAs were 230 EU. (C, F) Complete remission was achieved within 6 months following treatment with prednisolone (1 mg/kg/day) plus IV pulse cyclophosphamide (11 mg/kg monthly). At the time of this writing, she remains in remission on low-dose prednisolone without relapse of vasculitis nor progression of lung fibrosis.

some clinical findings. Subclinical pulmonary hemorrhage may have caused a restrictive lung defect in three siblings with a unique urticarial vasculitic syndrome.[13] Schnabel et al[14] reported an increased incidence of hemosiderin-laden macrophages in patients with ANCA-associated vasculitis and pulmonary disease compared with patients with CTD-associated interstitial lung disease. Patients with increased iron-positive macrophages had higher disease activity, a higher ANCA titer, a higher myeloperoxidase (MPO) concentration in the BAL fluid, and more frequent low-attenuation opacities on HRCT compared with patients with a low iron-positive cell count. Furthermore, idiopathic pulmonary hemosiderosis is characterized by diffuse alveolar hemorrhage with hemosiderin-laden macrophages, restrictive lung disease, and interstitial fibrosis.[15,16]

The second hypothesis that may explain lung fibrosis is that MPO-ANCAs play a direct role in the pathogenesis of PF. The constant positivity of anti-MPO antibodies in the reported case series and animal models[17] suggests a putative role for MPO-ANCAs in the pathogenesis of PF. ANCA antigens such as MPO undergo translocation to the surface of neutrophils (possibly in response to proinflammatory cytokines), and subsequent binding of circulating ANCAs results in neutrophil degranulation and the release of reactive oxygen species, causing injury and consequent fibrosis.[17–19] This hypothesis is further supported by the findings that in patients with rheumatoid arthritis (RA), ANCA positivity, essentially anti-MPO, was associated with more active disease, occurrence of vasculitis, and more extraarticular manifestations, including PF.[20,21]

Therapy

Data regarding therapy are limited to small retrospective studies with heterogeneous populations. Optimal therapy is controversial. A prospective multicenter trial for patients with newly diagnosed MPO-ANCA-associated vasculitis (J [Japanese] MAAV) was performed to evaluate the impact or immunosuppression therapy for remission induction (manuscript submitted).

Among 48 patients with MPO-ANCA-associated vasculitis, PF was identified in 22 patients (46%) at the diagnosis of vasculitis. Concomitant organ involvement included renal involvement in 15/22 (68%), peripheral neuropathy in two (9%), pulmonary-muscle syndrome in two (9%), and no extrapulmonary involvement in three (14%). Chest HRCT was performed in 21 patients before

remission-induction therapy. Lung fibrosis was found in 18 patients (86%). The most prevalent HRCT findings included honeycombing (52%), GGOs (48%), emphysema (38%), and consolidation (29%). It was notable that lung fibrosis of eight patients with emphysema corresponded to the recently proposed syndrome "combined PF and emphysema (CPFE)."[22] Following induction therapy, vital capacity improved >10% in approximately half of patients with PF, particularly when cyclophosphamide was included in the treatment regimen (manuscript in preparation). By contrast, in their cohort of 12 patients with ANCA-associated PF, none of 12 patients improved with immunosuppressive therapy. Furthermore, ANCA titers did not correlate with the course of vasculitis or evolution of fibrosis.[6]

The mechanisms responsible for lung fibrosis, ANCA production, and vasculitis may be multifactorial and interactive. The role of cofactors such as genetic background and environmental factors (particularly tobacco smoking) has not been elucidated. International prospective long-term studies are required to better define the pathogenesis of ANCA-associated lung fibrosis and facilitate development of effective therapy.

REFERENCES

1. 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(6): 847–856
2. 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(1):7–16
3. Gal AA, Salinas FF, Staton GW Jr. The clinical and pathological spectrum of antineutrophil cytoplasmic autoantibody-related pulmonary disease: a comparison between perinuclear and cytoplasmic antineutrophil cytoplasmic autoantibodies. Arch Pathol Lab Med 1994;118(12):1209–1214
4. Homma S, Matsushita H, Nakata K. Pulmonary fibrosis in myeloperoxidase antineutrophil cytoplasmic antibody-associated vasculitides. Respirology 2004;9(2):190–196
5. 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(4):407–415
6. Hervier B, Pagnoux C, Agard C, et al; 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(3):404–407
7. Foulon G, Delaval P, Valeyre D, et al. ANCA-associated lung fibrosis: analysis of 17 patients. Respir Med 2008;102(10): 1392–1398
8. Tzelepis GE, Kokosi M, Tzioufas A, et al. Prevalence and outcome of pulmonary fibrosis in microscopic polyangiitis. Eur Respir J 2010;36(1):116–121
9. American Thoracic Society. Idiopathic pulmonary fibrosis: diagnosis and treatment. International consensus statement. American Thoracic Society (ATS), and the European Respiratory Society (ERS). Am J Respir Crit Care Med 2000;161(2 Pt 1):646–664
10. Jennette JC, Falk RJ, Andrassy K, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994;37(2):187–192
11. 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(6):2065–2071
12. Eschun GM, Mink SN, Sharma S. Pulmonary interstitial fibrosis as a presenting manifestation in perinuclear antineutrophilic cytoplasmic antibody microscopic polyangiitis. Chest 2003;123(1):297–301
13. Al Riyami BM, Al Kaabi JK, Elagib EM, El Khatim HS, Woodhouse NJ. Subclinical pulmonary haemorrhage causing a restrictive lung defect in three siblings with a unique urticarial vasculitis syndrome. Clin Rheumatol 2003;22(4–5): 309–313
14. 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(1):118–124
15. Buschman DL, Ballard R. Progressive massive fibrosis associated with idiopathic pulmonary hemosiderosis. Chest 1993;104(1):293–295
16. Corrin B, Jagusch M, Dewar A, et al. Fine structural changes in idiopathic pulmonary haemosiderosis. J Pathol 1987; 153(3):249–256
17. Foucher P, Heeringa P, Petersen AH, et al. Antimyeloperoxidase-associated lung disease. An experimental model. Am J Respir Crit Care Med 1999;160(3):987–994
18. Falk RJ, Terrell RS, Charles LA, Jennette JC. Anti-neutrophil cytoplasmic autoantibodies induce neutrophils to degranulate and produce oxygen radicals in vitro. Proc Natl Acad Sci U S A 1990;87(11):4115–4119
19. Collins CE, Quismorio FP Jr. Pulmonary involvement in microscopic polyangiitis. Curr Opin Pulm Med 2005;11(5): 447–451
20. Cambridge G, Williams M, Leaker B, Corbett M, Smith CR. Anti-myeloperoxidase antibodies in patients with rheumatoid arthritis: prevalence, clinical correlates, and IgG subclass. Ann Rheum Dis 1994;53(1):24–29
21. Braun MG, Csernok E, Schmitt WH, Gross WL. Incidence, target antigens, and clinical implications of antineutrophil cytoplasmic antibodies in rheumatoid arthritis. J Rheumatol 1996;23(5):826–830
22. Cottin V, Nunes H, Brillet PY, et al; Groupe d'Etude et de Recherche sur les Maladies Orphelines Pulmonaires (GERM O P). Combined pulmonary fibrosis and emphysema: a distinct underrecognised entity. Eur Respir J 2005; 26(4):586–593