ANCA-Associated Vasculitis in a Patient with Chronic Thromboembolic Pulmonary Hypertension

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An 82-year-old woman with a history of chronic thromboembolic pulmonary hypertension (CTEPH) presented with malaise, left facial nerve paralysis and the positive seroconversion of myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA). She was diagnosed with ANCA-associated vasculitis (AAV). Administration of corticosteroids significantly improved her symptoms, with a decline in the serum MPO-ANCA level. Ten months later than the initial presentation, she developed an AAV exacerbation with lung infiltration and pericardial effusion, which improved with high-dose corticosteroid therapy. To date, a limited number of AAV cases concomitant with pulmonary hypertension have been reported. The case report presented herein suggests a potential role for CTEPH in the development of AAV.

Key words: chronic thromboembolic pulmonary hypertension, antineutrophil cytoplasmic antibody, ANCA-associated vasculitis, myeloperoxidase-ANCA

INTRODUCTION

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is characterized by damage to small- and medium-sized blood vessels and the detection of ANCA in serum. Pulmonary arterial hypertension may develop in patients with AAV, either concomitant with or as a complication of AAV. In some cases of pulmonary hypertension concomitant with AAV, immunosuppressive therapy for vasculitis improves pulmonary arterial hypertension. However, in other cases, especially those involving thrombi in the pulmonary artery, immunosuppressants are ineffective, suggesting various underlying pathologies in the pulmonary artery.

Herein, we report a case of myeloperoxidase (MPO)-ANCA-positive AAV which developed during treatment for chronic thromboembolic pulmonary hypertension (CTEPH). In the present case, CTEPH developed prior to the positive-seroconversion of MPO-ANCA and the clinical manifestations of AAV, suggesting that CTEPH plays a role in the development of AAV.

CASE REPORT

An 82-year-old woman was referred to Tokai University Hospital due to persistent malaise and left facial nerve paralysis; however, one year prior, she presented with hemoptysis and dyspnea on exertion, and was diagnosed with CTEPH based on: 1) increased mean pulmonary artery pressure (mPAP) of 24 mmHg and normal pulmonary capillary wedge pressure confirmed during a right heart catheterization study, 2) occlusion of the subsegmental pulmonary artery in the right upper lobe on computed tomography (CT) angiography, and 3) multiple segmental perfusion defects in the right upper and middle lobes with a normal ventilation pattern on nuclear medicine lung ventilation/perfusion scintigraphy (Fig. 1). There was no deep venous thrombosis in the lower extremities, and she had no risk factors for coagulopathy, such as malignancies, antiphospholipid syndrome, infection, or blood coagulation factor deficiency such as protein C or S. Serum C-reactive protein (CRP) was 0.46 mg/dL and MPO-ANCA was negative at that time. After initiating treatment for CTEPH including long-term oxygen therapy (LTOT) and anticoagulant therapy with edoxaban tosylate hydrate, the patient's mPAP gradually declined (Fig. 2).

Upon her referral, the patient had no physical or neurological abnormalities, except for left facial nerve paralysis. Laboratory tests showed the positive-seroconversion of MPO-ANCA (132 IU/mL) along with increased white blood cell counts (12,200/μL), of which eosinophils accounted for 3.5%, elevated serum levels of CRP (7.36 mg/dL) and Krebs-von-Lungen-6 (512 IU/mL). Neither proteinuria nor increased serum levels of D-dimer or creatinine were present. A thoracic CT scan showed a mosaic attenuation pattern consistent with CTEPH (Fig. 3). The patient was diagnosed with AAV based on the European Medicines Agency algorithm [1] and treated with low-dose oral prednisolone (15 mg per day, 0.3 mg/kg). Her symptoms markedly

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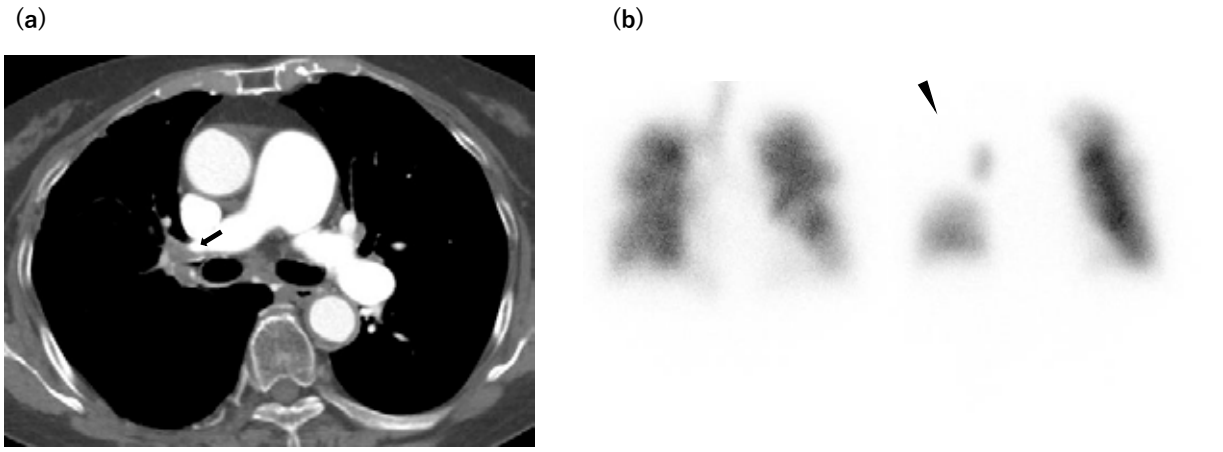

Fig. 1 Imaging for the diagnosis of chronic thromboembolic pulmonary hypertension: (a) Computed tomography angiogram of the chest showing thrombus (arrow) in the subsegmental pulmonary artery of right upper lobe; (b) Nuclear medicine lung ventilation with ^{81m}Kr gas (left) and perfusion with ^{99m}Tc macroaggregated albumin (right) scintigraphy showing multiple segmental perfusion defects (arrow heads) in the right upper and middle lobes, with a normal ventilation pattern.

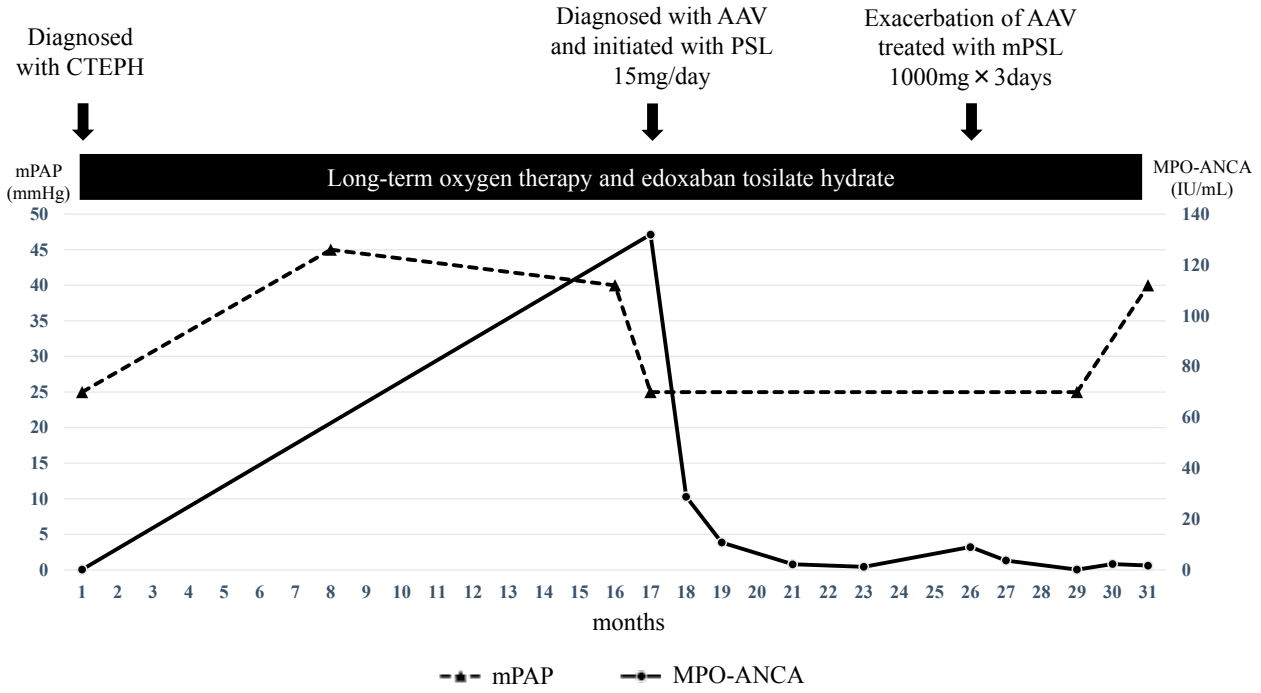

Fig. 2 Clinical course showing fluctuations of the mean pulmonary arterial pressure (mPAP) and the serum level of myeloperoxidase antineutrophil cytoplasmic antibody (MPO-ANCA) during the pharmacotherapy. CTEPH, chronic thrombotic pulmonary hypertension; AAV, antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis.

improved with a decline in serum MPO-ANCA levels.

Unfortunately, 10 months later than the introduction of prednisolone, when the dose of prednisolone was tapered to 6 mg per day, the patient developed progressive dyspnea and severe hypoxia and was hospitalized. CT images indicated an infiltrate in the right upper lobe and pericardial effusion, and the serum MPO-ANCA level was modestly increased (9.0 IU/mL). Transthoracic echocardiography showed no increase in the mPAP, therefore, the patient was diagnosed with an AAV exacerbation concomitant with pericarditis. Methylprednisolone pulse therapy (1,000 mg per day for 3 days) followed by high-dose prednisolone treatment (50 mg per day, 1 mg/kg) successfully improved the pericardial effusion as well as the patient's respiratory condition and lung opacity, as seen on CT images (Fig. 4). The patient was discharged without supplemental oxygen therapy. Subsequently, the dose of prednisolone was gradually tapered to 8 mg per day, and her serum MPO-ANCA remained negative.

DISCUSSION

We have reported a case of AAV that developed one year after the initial diagnosis of CTEPH. Venous thromboembolism (VTE) is a relatively common comorbidity of AAV, and pulmonary artery vasculitis may also occur in some patients with AAV. The present case, however, was unique as CTEPH preceded the

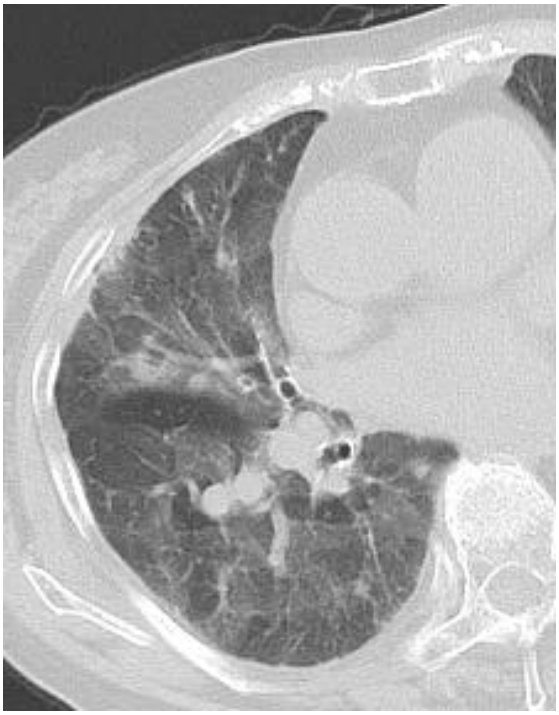

Fig. 3 High-resolution computed tomography scans showing mosaic attenuation pattern

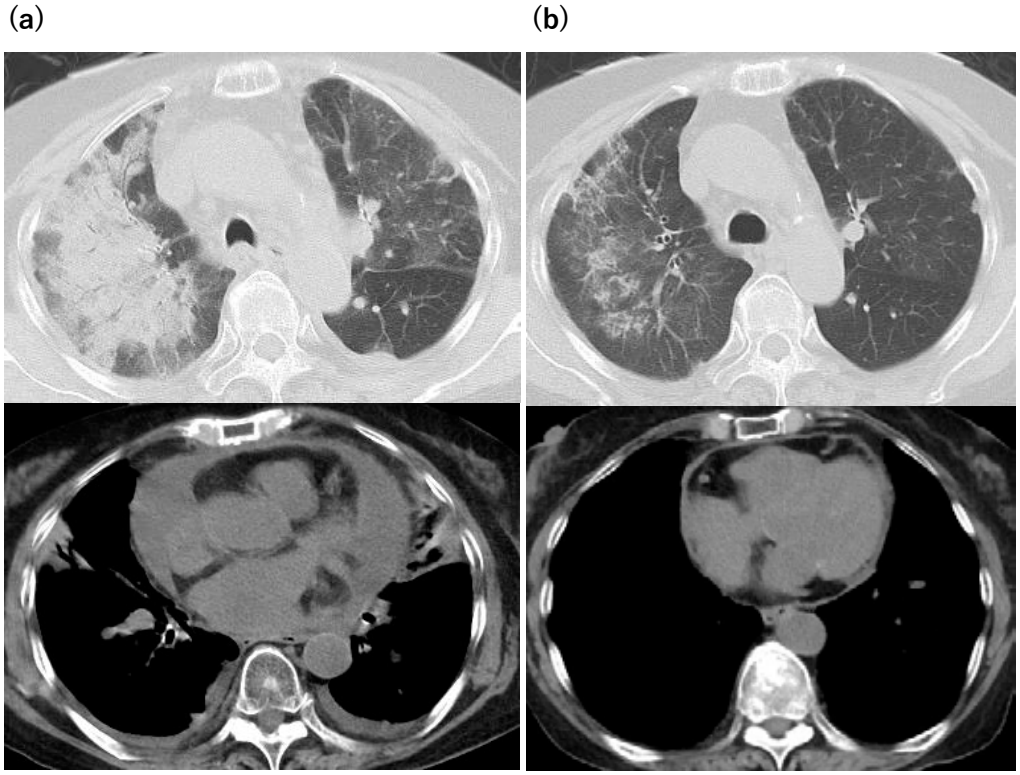

Fig. 4 Thoracic computed tomography (CT) scan at the antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis exacerbation: (a) Thoracic CT scan showing an infiltration in the right upper lobe and pericardial effusion; (b) After high-dose corticosteroid therapy, lung opacity and pericardial effusion were improved.

positive-seroconversion of MPO-ANCA and the clinical manifestations of AAV such as persistent malaise, left facial nerve paralysis, pulmonary opacity and pericardial effusion.

A number of predisposing factors of CTEPH such as a history of VTE, collagen vascular disease, malignancy, infection and hemostatic factor abnormalities have been reported [2]. VTE occurs in patients with AAV at a rate of 12.4% [3], or 7/100 person-years, which is higher than that in the general population (0.18/100 person-years) [4, 5]. VTE is also more likely to occur in patients with active AAV, although the incidence is still high during inactive periods (1.0/100 person-years) [6]. At the initial presentation of CTEPH,

Table 1 Cases of ANCA-associated vasculitis concomitant with pulmonary hypertension.

Authors (Years)	Age, Gender	Order of presentation	Thrombi in pulmonary arteries	PH state in response to AAV treatment	ANCA	Diagnosis interval between PH and AAV	CT findings
Present case	82, F	CTEPH → AAV	present	not improved	anti-MPO	1 year	mosaic attenuation
D Forde, *et al.* (2011) [9]	32, M	CTEPH → AAV	present	not improved	anti-PR3	4 months	mosaic attenuation
J Dion, *et al.* (2015) [8]	26, M	AAV → PH	absent	improved	negative	3 months	GGOs
Y Li, *et al.* (2015) [11]	21, F	Concomitant*	absent	improved	anti-MPO	-	GGOs and nodular opacities
D Launay, *et al.* (2006) [10]	33, M	AAV → PH	absent	improved	anti-PR3	6.5 years	excavated nodules
	49, M	AAV → PH	absent	not improved	cANCA	18 months	nodular opacities
	38, F	AAV → PH	absent	not improved	anti-MPO	4 years	alveolar hemorrhage
	49, M	PH → AAV	absent	NA**	anti-PR3	2 years	nodular opacities

*AAV was concomitant with pulmonary hypertension at the first presentation. **The PH state was not evaluated because the patient died from sepsis one week after the initiation of immunosuppressants. ANCA, antineutrophil cytoplasmic antibody; CTEPH, chronic thromboembolic pulmonary hypertension; PH, pulmonary hypertension other than CTEPH; AAV, ANCA-associated vasculitis; MPO, myeloperoxidase; PR3, proteinase3; cANCA, cytoplasmic ANCA; GGO, ground-glass opacity; NA, not available; CT, computed tomography.

however, the serum MPO-ANCA was negative and there were no symptoms suggestive of collagen vascular diseases including AAV. During the clinical course of 31 months, she did not present any sings of malignancies or infections. While there was no deep venous thrombosis in the lower extremities, an observational study reported that 30% of patients diagnosed with CTEPH were presented without the evidence of VTE [7]. As we examined the only traditional risk factors for VTE such as protein C or S deficiency and anti-phospholipid antibodies, other unexamined hemostatic factor abnormalities including elevated coagulation factor VIII and von Willebrand factor, fibrinogen gene polymorphisms may possibly have contributed to the formation of thrombi in pulmonary artery.

In contrast, pulmonary hypertension is rarely accompanied by AAV. To date, only seven cases of pulmonary hypertension with AAV have been reported [8–11]. In five of these cases, AAV developed prior to or concomitant with pulmonary hypertension, with the interval between the diagnosis of AAV and pulmonary hypertension ranging from 3 months to 6.5 years (Table 1). Of note, three patients without thrombi responded well to the immunosuppressive drugs for AAV with a significant decrease in mPAP, suggesting the involvement of pulmonary artery vasculitis. Conversely, two patients with CTEPH including the present case did not show an apparent improvement in pulmonary hypertension in response to AAV treatments, implying different underlying pathogenesis from that of PH without the involvement of thrombi.

In the present case, we observed a modest decline in the mPAP during the course of treatment. However, this result may be due to LTOT and edoxaban tosylate hydrate, and not the systemic corticosteroid treatment. The patient presented herein was diagnosed with CTEPH one year prior to the onset of AAV with the positive-seroconversion of MPO-ANCA and the clinical manifestations. A previous study reported that VTE can also occur before a diagnosis of AAV [12]. These observations suggest that pulmonary hypertension and/or thromboembolic events may induce immunological reactions that result in the production of MPO-ANCA.

Neutrophilic inflammation has been implicated in the pathogenesis of venous thrombosis and pulmonary hypertension, including CTEPH [13–15], in which activated neutrophils release MPO-containing neutrophil extracellular traps (NETs) [16, 17]. One study showed elevated levels of MPO in the plasma of patients with CTEPH compared to those in healthy controls, and extensive areas of NETosis in vascularized intrapulmonary thrombi and occlusive plexiform lesions [18]. It is well known that the presence of interstitial lung disease is occasionally followed by seroconversion to MPO-ANCA positivity [19], suggesting that chronic inflammation may be a source of MPO-ANCA. In the present case, we observed the evidence of low-grade inflammation until the onset of AAV. Given that the specific antigens to ANCA are highly expressed in the lungs of patients with CTEPH and other types of pulmonary hypertension, pulmonary hypertension might actually have contributed to the ANCA production, potentially affecting the subsequent development of AAV. Clinicians should be vigilant with and implement close monitoring for signs of potential AAV development in patients with CTEPH.

We have reported a case of MPO-ANCA-positive AAV which occurred one year after the initial diagnosis of CTEPH. As pathological involvement of neutrophilic inflammation has been suggested, AAV can develop during follow-up of patients with pulmonary hypertension such as CTEPH.

DECLARATION OF INTEREST

The authors have no conflicts of interest to declare.

REFERENCES

1) Watts, R., Lane, S., Hanslik, T., Hauser, T., Hellmich, B., Koldingsnes, W. *et al*. Development and validation of a consensus methodology for the classification of the ANCA-associated vasculitides and polyarteritis nodosa for epidemiological studies. Ann Rheum Dis 2007; 66: 222–7.
2) Kim, N. H. & Lang, I. M. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir Rev 2012; 21: 27–31.
3) Hansrivijit, P., Trongtorsak, A., Gadhiya, K. P., Lnu, K., Dimech, C. T., Thongprayoon, C. *et al*. Incidence and risk factors of venous thromboembolism in ANCA-associated vasculitis: a meta-analysis and metaregression. Clin Rheumatol 2021; 40: 2843–53.
4) Hansson, P. O., Welin, L., Tibblin, G. & Eriksson, H. Deep vein thrombosis and pulmonary embolism in the general population. 'The Study of Men Born in 1913'. Arch Intern Med 1997; 157: 1665–70.
5) Merkel, P. A., Lo, G. H., Holbrook, J. T., Tibbs, A. K., Allen, N. B., Davis, J. C., Jr. *et al*. Brief communication: high incidence of venous thrombotic events among patients with Wegener granulomatosis: the Wegener's Clinical Occurrence of Thrombosis (WeCLOT) Study. Ann Intern Med 2005; 142: 620–6.
6) Stassen, P. M., Derks, R. P., Kallenberg, C. G. & Stegeman, C. A. Venous thromboembolism in ANCA-associated vasculitis--incidence and risk factors. Rheumatology (Oxford) 2008; 47: 530–4.
7) Bonderman, D., Wilkens, H., Wakounig, S., Schäfers, H. J., Jansa, P., Lindner, J. *et al*. Risk factors for chronic thromboembolic pulmonary hypertension. Eur Respir J 2009; 33: 325–31.
8) Dion, J., Terrier, B., Jaïs, X., Mehdaoui, A., Sattler, C., Amar, D. *et al*. Atypical vasculitis mimicking chronic thromboembolic pulmonary hypertension. Am J Med 2015; 128: e47–9.
9) Forde, D. G., McCullagh, B., Henry, M. T., Gaine, S. P. & Murphy, D. M. Chronic thromboembolic disease and necrotizing granulomatous vasculitis–A case report. Respiratory Medicine CME 2011; 4: 149–50.
10) Launay, D., Souza, R., Guillevin, L., Hachulla, E., Pouchot, J., Simonneau, G. *et al*. Pulmonary arterial hypertension in ANCA-associated vasculitis. Sarcoidosis Vasc Diffuse Lung Dis 2006; 23: 223–8.
11) Li, Y. & Yi, Q. Pulmonary arterial hypertension associated with rare cause of ANCA-associated vasculitis misdiagnosed as idiopathic one. Int J Clin Exp Med 2015; 8: 16850–3.
12) Henry, N., Brilland, B., Wacrenier, S., Djema, A., Garnier, A. S., Gansey, R. *et al*. Incidence and Risk Factors of Venous Thromboembolic Events in Patients with ANCA-Glomerulonephritis: A Cohort Study from the Maine-Anjou Registry. J Clin Med 2020; 9.
13) Kapoor, S., Opneja, A. & Nayak, L. The role of neutrophils in thrombosis. Thromb Res 2018; 170: 87–96.
14) Quarck, R., Wynants, M., Verbeken, E., Meyns, B. & Delcroix, M. Contribution of inflammation and impaired angiogenesis to the pathobiology of chronic thromboembolic pulmonary hypertension. Eur Respir J 2015; 46: 431–43.
15) Taylor, S., Dirir, O., Zamanian, R. T., Rabinovitch, M. & Thompson, A. A. R. The Role of Neutrophils and Neutrophil Elastase in Pulmonary Arterial Hypertension. Front Med (Lausanne) 2018; 5: 217.
16) Jennette, J. C., Falk, R. J., Hu, P. & Xiao, H. Pathogenesis of antineutrophil cytoplasmic autoantibody-associated small-vessel vasculitis. Annu Rev Pathol 2013; 8: 139–60.
17) Nakazawa, D., Masuda, S., Tomaru, U. & Ishizu, A. Pathogenesis and therapeutic interventions for ANCA-associated vasculitis. Nat Rev Rheumatol 2019; 15: 91–101.
18) Aldabbous, L., Abdul-Salam, V., McKinnon, T., Duluc, L., Pepke-Zaba, J., Southwood, M. *et al*. Neutrophil Extracellular Traps Promote Angiogenesis: Evidence From Vascular Pathology in Pulmonary Hypertension. Arterioscler Thromb Vasc Biol 2016; 36: 2078–87.
19) Katsumata, Y., Kawaguchi, Y. & Yamanaka, H. Interstitial Lung Disease with ANCA-associated Vasculitis. Clin Med Insights Circ Respir Pulm Med 2015; 9: 51–6.