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MPO-ANCA positive interstitial pneumonia: Current knowledge and future perspectives

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Abstract. Although interstitial pneumonia is an important respiratory manifestation in microscopic polyangiitis (MPA), no studies have examined the detailed pathogenesis of interstitial pneumonia during the clinical course of MPA. In addition, it is considered that MPA develops at a certain incidence rate from myeloperoxidase (MPO)-antineutrophil cytoplasmic antibody (ANCA) positive interstitial pneumonia. However, there is a lack of consensus among pulmonologist and rheumatologist regarding whether MPO-ANCA positive interstitial pneumonia, which does not accompany other organ damage related to ANCA-associated vasculitis (AAV) other than interstitial pneumonia, should be included in AAV. In this review article, the clinical questions regarding MPO-ANCA positive interstitial pneumonia have been set, and evidence to date and problems to be solved in future are outlined.

Introduction

Pulmonary alveolar hemorrhage and interstitial pneumonia are typical respiratory manifestations in microscopic polyangiitis (MPA), which is one of antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) (1-4). Alveolar hemorrhage is widely recognized as a respiratory lesion associated with vasculitis (5). However, at present, the involvement of myeloperoxidase (MPO)-ANCA in the development and progression of interstitial pneumonia and its clinical significance remains unclear. A prospective study of the severity-based treatment protocol for Japanese patients with MPO-ANCA-associated vasculitis (JMAAV) (6), where AAV without organ damage other than lung lesions was defined as a pulmonary-limited type of AAV, reported that six of 48 MPO-ANCA positive AAV (MPO-AAV) cases (12.5%) were pulmonary-limited AAV. Thus, MPO-ANCA positive interstitial pneumonia includes interstitial pneumonia associated with MPO-AAV such as MPA, and interstitial pneumonia with positive MPO-ANCA without vasculitic lesions in systemic organs. The former is comprised of two types: MPO-AAV in which interstitial pneumonia and vasculitis are diagnosed simultaneously and MPO-AAV with preceding interstitial pneumonia in which vasculitis becomes apparent during the course of interstitial pneumonia. However, there is a lack of sufficient consensus among respiratory specialists and vasculitis specialists regarding whether MPO-ANCA positive interstitial pneumonia, which does not accompany other organ damage related to AAV other than interstitial pneumonia, should be included in AAV (7).

Based on these considerations, the following three clinical questions (CQs) regarding MPO-ANCA

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positive interstitial pneumonia have been set, and evidence to date and problems to be solved in future are outlined in this review article.

CQ 1: Can MPA or MPO-ANCA cause interstitial pneumonia?

CQ 2: Can MPO-ANCA positive interstitial pneumonia cause MPA?

CQ 3: Can interstitial pneumonia trigger MPO-ANCA production?

Epidemiology

Interstitial pneumonia in MPA (Table 1) (6, 8-16)

Arimura *et al.* (8) reported interstitial pneumonia in nine of 17 MPA cases (52.9%) and the frequency of interstitial pneumonia in MPA was 26.2 to 47.4% in subsequent domestic reports (6, 9, 10) and 7.2 to 42.5% in overseas reports (11-16). The most common age of onset of interstitial pneumonia was between 50 and 60 years, being slightly more common in males and smokers. Although the most common imaging finding is a usual interstitial pneumonia (UIP) pattern, a variety of findings including nonspecific interstitial pneumonia (NSIP) pattern and combined pulmonary fibrosis and emphysema (CPFE) pattern may also be seen. Suzuki *et al.* (17) demonstrated the increased attenuation around honeycombing or traction bronchiectasis in MPA patients with UIP pattern in chest high-resolution CT (HRCT). It was also reported that complications of interstitial pneumonia affect the long-term vital prognosis of patients with MPA (10, 11). Maillet *et al.* (18) reported that age > 65 years at AAV diagnosis, alveolar hemorrhage at AAV diagnosis and UIP pattern were the significant factors independently associated with shorter survival in AAV patients with interstitial lung disease. Recently, Hozumi *et al.* (19) reported that a lower percent-predicted forced vital capacity was independently associated with a higher mortality rate and a higher acute exacerbation of interstitial pneumonia incidence rate in MPA patients with interstitial pneumonia.

Although interstitial pneumonia is an important lesion in MPA, no studies have examined the detailed pathogenesis of interstitial pneumonia during the clinical course of MPA; therefore, prospective observational studies of MPA without interstitial pneumonia are necessary to clarify CQ 1.

MPO-ANCA in idiopathic interstitial pneumonias (Table 2) (20-27)

Ando *et al.* (22) examined the clinical course of 61 consecutive cases diagnosed as idiopathic pulmonary fibrosis (IPF) and found that only three (4.9%) patients were MPO-ANCA positive at the initial visit, six (9.8%) patients changed from MPO-ANCA negative to positive during the course of the disease, and two (22.2%) of nine MPO-ANCA positive IPF patients developed MPA during the course of the disease. Furthermore, Kagiyama *et al.* (23) reported that 20 of 504 (4.0%) IPF patients were MPO-ANCA positive at the initial visit, 15 of 264 (5.7%) became positive during the course of the disease, and nine of 35 (25.7%) MPO-ANCA positive IPF patients developed MPA. Similarly, Hozumi *et al.* (25) found that 16 of 305 idiopathic interstitial pneumonias (IIPs) (5.2%) were MPO-ANCA positive at the first visit, 10 (3.3%) became MPO-ANCA positive during the disease course, and 9 (24.3%) developed MPA during a 5-year observation period. That study identified two risk factors for MPA: UIP pattern and no treatment for IIPs. An overseas, retrospective study of ANCA positivity in patients with IPF in a North American population by Liu *et al.* (26) reported that six of 353 (1.7%) IPF patients in an exploratory cohort and 12 of 392 (3.0%) in a validation and replication cohort were positive for MPO-ANCA at diagnosis. In addition, among the MPO-ANCA-positive patients, two of six (33%) in the exploratory cohort and three of 12 (25%) in the validation replication cohort subsequently developed vasculitis; however, there was no significant difference in the median non-transplant survival between ANCA-positive and ANCA-negative patients.

Based on the observations, although the number of ANCA-positive cases among IPF patients in North America was lower than that in Japan, it is considered that MPA develops at a certain incidence rate from MPO-ANCA positive interstitial pneumonia (CQ 2).

Table 1. Characteristics of main articles describing the AAV(MPA)-ILD

Country	Author	Year	Ref.	Patients, n	ILD, n (%)	Age	Sex Male (%)	ANCA pattern (MPO/PR3)	Follow-up period (months)	MST (months)	1-yr/5-yr survival (%)	Mortality (%)
Japan	Arimura Y	1995	8	MPO-ANCA(+), 46 MPA, 17	20 (43.5) 9 (52.9)	NR	NR	MPO	NR	NR	NR	42.9 (n=28)
Japan	Ozaki S	2012	6	MPO-AAV, 48	22 (45.8)	NR	NR	MPO	18	NR	NR	NR
Japan	Sada K	2014	9	MPA/RLV, 78	37(47.4)	NR	NR	MPO 76 PR3 2	NR	NR	NR	NR
Japan	Hirayama K	2015	10	AAV + RPGN, 1147	301 (26.2)	67.8	140 (47.6)	MPO 1088 PR-3 114	NR	NR	69.9/50.2	NR
Greece	Tzelepis GE	2010	11	MPA, 33	13 (39.4)	57	9 (69)	P 32 C 1	NR	72	NR	46.2 (n=6)
UK	Arulkumaran N	2011	12	MPA, 194	14 (7.2)	67.3	10 (71.4)	MPO	NR	NR	50.0/29.0	NR
France	Comarmond C	2014	13	AAV+PF	49 MPA 40 GPA 9	68	30 (61.2)	MPO 43 PR-3 2	48	NR	NR	36.7 (n=18)
Mexico	Flores-Suárez LF	2015	14	MPA, 40	17 (42.5)	54.2	9 (52.9)	MPO 36 PR-3 2	NR	104	NR	41.1 (n=7)
Argentina	Casares MF	2015	15	MPA, 28	9 (32.1)	60	5 (55.6)	NR	76	NR	NR	44.4 (n=4)
Sweden	Mohammad AJ	2017	16	MPA, 61 GPA, 79	8 (13.1) 2 (2.5)	NR NR	NR NR	NR	NR	NR	NR	NR

AAV: ANCA-associated vasculitis, ANCA: anti-neutrophil cytoplasmic antibody, GPA: granulomatosis with polyangiitis, ILD: interstitial lung disease, MPA: microscopic polyangiitis, MPO: myeloperoxidase, MST: median survival time, NR no records, PLV: pulmonary-limited vasculitis, PR3: proteinase 3, RPGN: rapidly progressive glomerulonephritis

Table 2. MPO-ANCA positivity in IIPs

Country	Author	Year	Ref.	Patients, n	MPO-ANCA(+) Total, n (%)	Initial, n (%)	In progress, n (%)	Age	Sex Male (%)	Onset of MPA, n (%)	MST (month) 1-yr/5-yr survival	Mortality (%)
Japan	Homma S	2004	[208]	MPO-ANCA IP, 31 (MPA-IP, 8)	NR	NR	NR	69	17 (54.8)	NR	5-yr, 50%	41.9 (n=13)
Japan	Tanaka T	2012	[2119]	MPO-ANCA IP, 9	NR	NR	NR	62.1	6 (66.7)	0	NR	44.4 (n=4)
Japan	Ando M	2013	[22019]	IPF, 61	9 (14.8%)	3	6	69	9 (100)	2 (22)	MST 62	66.7 (n=6)
Japan	Kagiyama N	2015	[2130]	IPF, 504 504 → 264	35 (6.9%)	20	15	71.4	11 (55.0)	9 (25.7) 3 (15) All PSL (-)	5-yr, 51.3%	NR
Japan	Hosoda C	2016	[2241]	IPF/UIP, 108	12 (11.1%)	11	1	65.2	8 (66.7)	3 (25)	MST 132	NR
Japan	Hozumi H	2018	[2352]	IIPs, 305	26 (8.5%)	16	10	NR	20 (76.9)	9 (24.3)	5-yr, 81.5	NR
US	Liu GY	2019	[2463]	IPF ① 353 ② 392	6 (1.7%) <PR-3 8> 12 (3.0%) <PR-3 2>	NR NR	NR NR	64.8 68.8	2 (33.3) 4 (33.3)	2 (33.3) 0 (0) 4 (33.3) 0 (0)	MST 60	NR
US	Baqir M	2019	[2574]	MPO-ANCA ILD, 18 (MPA-IP, 11)	NR	NR	NR	58.0	8 (55.5)	3 (42.0)	MST 66	50 (n=9)

ANCA: anti-neutrophil cytoplasmic antibody, IIPs: idiopathic pulmonary fibrosis, ILD: interstitial lung disease, IP: interstitial pneumonia, MPA: microscopic polyangiitis, MPO: myeloperoxidase, MST: median survival time, NR no records, PR3: proteinase 3, PSL: prednisolone, UIP: usual interstitial pneumonia

Relationship between MPO-ANCA production and interstitial pneumonia

It has been proposed that MPO-ANCA is not only a useful disease marker for the diagnosis and classification of AAV, but might also be directly involved in the onset and progression of AAV as a pathogenic factor (28). MPO-ANCA can be induced by drugs, dust inhalation, smoking, silica and heavy metal exposure, and drugs and other factors are considered environmental factors in the development of AAV. Therefore, it is hypothesized that inflammatory cytokines such as tumor necrosis factor (TNF) produced by various stimuli induce MPO expression on the neutrophil cell membrane. ANCA binds to the MPO and induces excessive activation of neutrophils, which leads to the further abnormal production of cytokines causing vascular endothelial cell damage and vasculitis (ANCA-cytokine sequence theory) (29).

Recently, it was reported that one of the mechanisms of MPO-ANCA production involves the formation and abnormal degradation of neutrophil extracellular traps (NETs) due to infection or drugs (30, 31). NETs are a new neutrophil function reported by Brinkmann (32) in 2004, in which neutrophils release DNA fibers modified with bactericidal proteins, such as MPO and elastase, which play an important role in innate immunity. However, NETs are involved in the production of pathogenic autoantibodies, and therefore MPO-ANCA may be produced due to a decrease in NETs degradation. Furthermore, it was reported that binding of MPO-ANCA to MPO on the plasma membrane of activated neutrophils induce NETs formation. In the lungs, NETs-forming cells increased by stimulation with tobacco or bleomycin, have an activation/differentiation-inducing action on lung fibroblasts, and NETs were present in lung tissues near lung fibroblasts in patients with interstitial pneumonia (33). Recently, the presence of MPO-ANCA reactivity in the sputum of patients with serum ANCA-negative eosinophilic granulomatosis with polyangiitis was reported (34). Based on the above, chronic inflammation and fibrotic lesions in the lungs, including interstitial pneumonia, may be one of the sites of MPO-ANCA production induced by NETs.

Namba *et al.* (35) reported a significant association of *MUC5B* promotor variant rs35705950, the strongest susceptibility variant to IPF, with MPO-AAV-associated interstitial lung disease (ILD) in Japanese patients, but not with MPO-AAV without ILD. Kawasaki *et al*. (36) reported that IPF risk alleles *TERT* rs2736100A and *DSP* rs2076295G are associated with susceptibility to MPA and MPO-AAV, but no significant association was detected when the allele frequencies were compared between MPO-AAV patients with and without ILD. These data indicate that MPO-AAV-associated ILD or MPO-AAV share some susceptibility genes with IPF and may explain a high prevalence of interstitial pneumonia in patients with MPO-AAV.

In recent years, stimulation of neutrophils and T cells by activated macrophages and dendritic cells as a result of inflammation in lung tissues caused by smoking, the inhalation of silica or dust, or pathogenic microorganisms as well as the activation of peptidyl arginine deaminase promoting protein citrullination and the production of anti-CCP antibodies, has received attention as a pathogenic mechanism of rheumatoid arthritis (37). However, the presence of MPO-ANCA in localized lung areas in MPO-ANCA-positive interstitial pneumonia has not been previously investigated, and whether interstitial pneumonia is directly involved in MPO-ANCA production (CQ 3) is a research question that should be addressed in future.

MPO-ANCA positive interstitial pneumonia: differences from MPO-ANCA negative interstitial pneumonia based on radiological and pathological findings

In pathological findings from lung biopsy and autopsy in Japanese patients with MPO-ANCA positive interstitial pneumonia, Hebisawa *et al.* (38) demonstrated the high prevalence of UIP pattern, frequently with combined NSIP pattern. Hosoda *et al.* (24) compared the high-resolution CT (HRCT) and histopathological findings of MPA-naive interstitial pneumonia with MPO-ANCA positive UIP pattern and MPO-ANCA negative IPF and found no

significant difference in the frequency of honeycomb lung or emphysematous changes between the two groups. However, they reported that interstitial pneumonia with MPO-ANCA positive UIP pattern had a higher frequency of honeycombed lungs and increased lung field density around cysts compared with IPF. Furthermore, pathological findings of surgical lung biopsy specimens included plasma cell infiltration, inflammatory changes in the interstitium, lymphoid follicle formation with a germinal center, and a higher degree (grade) of cysts and cellular bronchiolitis. Baqir *et al.* (27) also examined imaging and pathological findings of 18 cases of MPO-ANCA positive interstitial pneumonia experienced at the Mayo clinic and reported no typical imaging or pathological findings in IPF.

Based on the above, radiological and pathological findings of MPO-ANCA positive and negative interstitial pneumonia may differ, and the significance of MPO-ANCA in interstitial pneumonia (CQ 2, 3) needs further investigation.

MPO-ANCA positive interstitial pneumonia from the perspective of pulmonologists and non-pulmonologists

A questionnaire survey on interdisciplinary cooperation in AAV and MPO-ANCA positive interstitial pneumonia was conducted at respiratory and non-respiratory specialist facilities; 29 facilities in the Ministry of Health, Labour, and Welfare, the Study Group on Diffuse Pulmonary Disorders, Scientific Research/Research on Intractable Diseases, and 31 facilities in the Japan Research Committee of the Ministry of Health, Labour, and Welfare for Intractable Vasculitis (7). A question regarding departments that mainly provide or should provide AAV care, 86% of the respiratory specialty facilities answered "department of rheumatology". In addition, 94% of the non-respiratory specialty facilities also answered "department of rheumatology". The results showed that "department of rheumatology" is considered the primary department in charge of AAV care, and there was no difference in perception between respiratory specialists and non-respiratory specialists regarding interdisciplinary cooperation for AAV.

Assessment of lung lesions (asymptomatic and symptomatic interstitial pneumonia and alveolar hemorrhage)

Whether asymptomatic or symptomatic interstitial pneumonia and alveolar hemorrhage should be the responsibility of different departments, all respiratory specialist facilities answered that any lung lesion was the responsibility of their own department (respiratory medicine department). However, 74% of the facilities in the vasculitis group (non-respiratory specialist facilities) reported that asymptomatic interstitial pneumonia was the responsibility of their department, 84% for symptomatic interstitial pneumonia, and 84% for alveolar hemorrhage. In terms of pulmonary lesions for which non-respiratory medicine departments consulted a respiratory medicine department, 39% of facilities reported consulting a respiratory medicine department for asymptomatic interstitial pneumonia, 68% for symptomatic interstitial pneumonia, and 71% for alveolar hemorrhage (Figure 1A). As described above, the interdisciplinary cooperation for AAV treatment varied depending on the treatment system of each medical institution, but the current situation is that symptomatic interstitial pneumonia and alveolar hemorrhage, which are symptomatic and require treatment, are treated through interdisciplinary cooperation with the respiratory medicine department. However, in the case of asymptomatic interstitial pneumonia, more than half of the non-respiratory specialist facilities do not collaborate with a respiratory medicine department; therefore, the need for inter-departmental collaboration in this area is considered an issue for future study.

Relationship between MPO-ANCA positive interstitial pneumonia and AAV in the absence of other organ involvement

MPO-ANCA positive interstitial pneumonia without other organ involvement was considered pulmonary-limited AAV and IIPs in 34% and 28% of respiratory specialist facilities, respectively. However, 64% of the non-respiratory specialist facilities considered MPO-ANCA positive interstitial pneumonia without involvement of other organs as pulmonary-limited

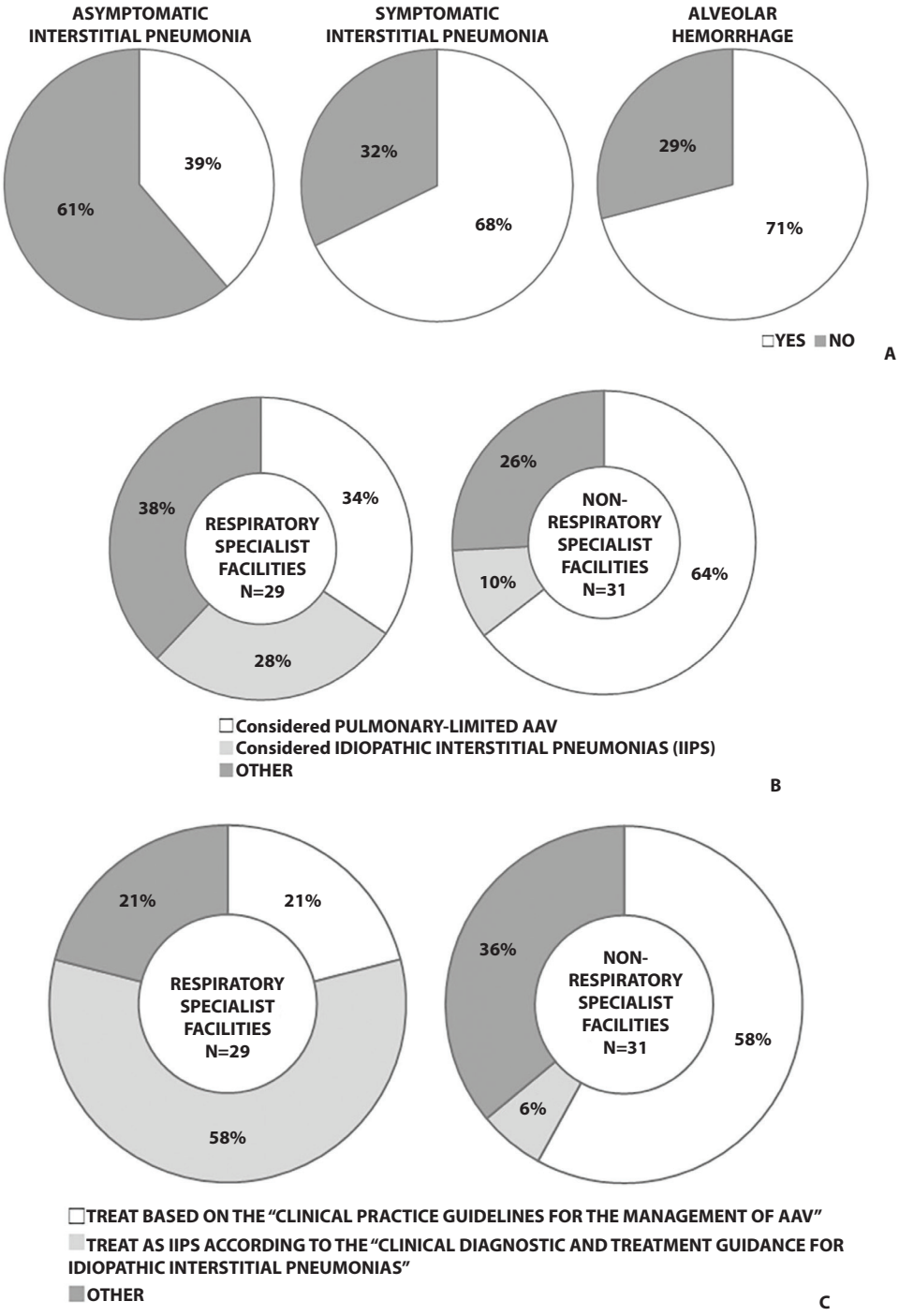

Figure 1. MPO-ANCA positive interstitial pneumonia from the perspective of pulmonologists and non-pulmonologists

(A) Assessment of lung lesions (asymptomatic and symptomatic interstitial pneumonia and alveolar hemorrhage) in non-pulmonologists. Question: Do you consult a respiratory physician regarding pulmonary lesions associated with MPA? **(B)** Relationship between MPO-ANCA positive interstitial pneumonia and AAV in the absence of other organ involvement. Question: What do you think about the relationship between MPO-ANCA positive interstitial pneumonia and AAV in the absence of other organ involvement? **(C)** Treatment of MPO-ANCA positive interstitial pneumonia without AAV. Question: How do you treat MPO-ANCA positive interstitial pneumonia without AAV?

AAV: ANCA-associated vasculitis, **ANCA:** anti-neutrophil cytoplasmic antibody, IIPs: idiopathic interstitial pneumonias, **MPA:** microscopic polyangiitis, MPO: myeloperoxidase

AAV, and 10% of the facilities considered it as IIPs (Figure 1B). MPO-ANCA positive interstitial pneumonia without the involvement of other organs was considered by many non-respiratory specialist facilities as pulmonary-limited AAV when compared with respiratory specialist facilities. The reason for considering the disease as pulmonary-limited AAV is that some cases may develop systemic AAV during the course of the disease. However, there was an opinion that the reason for considering it IIPs is that it often shows the UIP pattern, and antifibrotic drugs are a treatment option. Another respondent answered that although about 25% of MPO-ANCA positive interstitial pneumonia cases develop AAV during the disease course, many cases do not develop MPA; therefore, they might be considered IIPs.

Treatment of MPO-ANCA positive interstitial pneumonia without AAV

Twenty-one percent of the respiratory specialist facilities responded that they treat patients based on the "Clinical practice guidelines for the management of AAV." (39), and 58% of the facilities responded that they treat patients as IIPs by referring to the "Clinical diagnostic and treatment guidance for idiopathic interstitial pneumonias" (40). Furthermore, 58% of the non-respiratory specialist facilities indicated that they would treat patients based on the "Clinical practice guidelines for the management of AAV", and 6% of the facilities indicated that they would treat patients as IIPs based on the "Clinical diagnostic and treatment guidance for idiopathic interstitial pneumonias" (Figure 1C). This difference may reflect differences in the way the disease concept of MPO-ANCA positive interstitial pneumonia without AAV is perceived as well as differences in specialties.

Treatment strategies of MPO-ANCA positive interstitial pneumonia

As mentioned above, MPO-ANCA positive interstitial pneumonia includes interstitial pneumonia associated with MPO-AAV and interstitial pneumonia in which no vasculitis lesions are found in systemic organs even if MPO-ANCA is positive. Therefore, it is necessary to assume two patterns and construct a treatment strategy accordingly.

When interstitial pneumonia with MPO-AAV is diagnosed, treatment should be based on organ involvements of vasculitis. "Clinical practice guidelines for the management of AAV" (39) is helpful to determine treatments. Comarmond *et al.* (13) described the induction of remission with steroids alone as a risk factor for death in interstitial pneumonia caused by MPO-AAV. Furthermore, the JMAAV study (6) reported improvement of interstitial pneumonia when patients were treated with intravenous cyclophosphamide (IVCY). When IVCY is not available, the oral administration of cyclophosphamide should be considered. However, in cases of MPO-ANCA positive interstitial pneumonia without MPO-AAV, treatment should be considered for IIPs, referring to the "Clinical diagnostic and treatment guidance for idiopathic interstitial pneumonias" (40). Hozumi *et al.* (25) reported no treatment for IIPs was a risk of developing MPA in MPO-ANCA positive interstitial pneumonia without MPO-AAV (hazard ratio, 3.52; 95% confidence interval, 1.42 to 15.9; $p = 0.01$). Treatment strategies for IIPs differ significantly between IPF with the highest prevalence and the poorest prognosis, and other diseases (non-IPF). Specifically, the antifibrotic drugs pirfenidone or nintedanib should be considered for the chronic phase treatment of IPF (41). However, the clinical course and prognosis of MPO-ANCA positive IPF may differ from that of MPO-ANCA negative IPF, and glucocorticoids and immunosuppressive drug therapy similar to MPA may be selected. At the time of acute exacerbation, methyprednisolone pulse therapy is given, and immunosuppressants may be used in combination (40). For the NSIP pattern of interstitial pneumonia, glucocorticoids monotherapy or a combination of glucocorticoids and immunosuppressive drugs is used (40). However, treatment strategies for MPO-ANCA positive interstitial pneumonia without AAV have not been established, and further studies are needed to determine the efficacy and safety of early-phase glucocorticoids and immunosuppressive therapies, indications for methotrexate, rituximab, and antifibrotic agents, treatment duration, and timing of dose reduction and discontinuation.

Future issues

MPO-ANCA measurement method

Although the internationally recommended primary measurement methods for ANCA is enzyme immunoassay (42), various reagents are used worldwide. Currently, cases with low MPO-ANCA titers may be judged as false positives or false negatives depending on a test method used because of differences in antigen purification methods, antigen epitope recognition sites in solid-phase methods, and cutoff values and measurement ranges due to the lack of uniformity in international units and standard sera among companies. In the future, it will be important to unify the evaluation method for ANCA measurement as well as the titers when evaluating MPO-ANCA.

MPO-ANCA positive interstitial pneumonia and interstitial pneumonia with autoimmune features

Clinical picture, course, and prognosis of a group of patients showing symptoms and test results related to collagen diseases without definite diagnosis have attracted recent attention. Consequently, three disease concepts have been proposed: undifferentiated CTD (UCTD) (43), lung dominant CTD (LD-CTD) (44), and autoimmune-featured interstitial lung disease (AIF-ILD) (45). Among them, only AIF-ILD includes ANCA as a measurement item for autoantibodies because of its high disease specificity. Subsequently, the American Thoracic Society (ATS) and the European Respiratory Society (ERS) proposed a new nomenclature, interstitial pneumonia with autoimmune features (IPAF) (46), and the classification criteria were developed that integrated the three disease concepts. IPAF does not include ANCA in the serological domain because it is associated with vasculitis rather than the CTD-associated ILD spectra of disorders. Currently, it has been suggested that ANCA should be added to the diagnostic criteria for IPAF because of the possibility of ANCA-associated interstitial pneumonia without vasculitis (47), and future trends will be closely watched.

Establishment of an international research collaboration scheme

Figure 2 shows the disease concept and related CQs of MPO-ANCA positive interstitial pneumonia

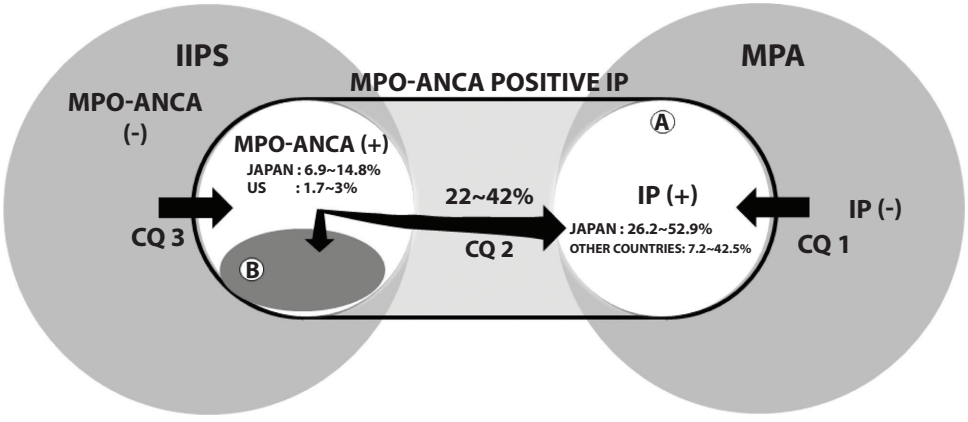

Figure 2. Disease concept and related CQs for
CQ 1: Can MPA or MPO-ANCA cause IP?
CQ 2: Can MPO-ANCA positive IP cause MPA?
CQ 3: Can IP trigger MPO-ANCA production?
A: MPA or MPO-AAV associated IP
B: MPO-ANCA associated IP without MPA or MPO-AAV
AAV: ANCA-associated vasculitis, **ANCA:** anti-neutrophil cytoplasmic antibody, **CQs:** clinical questions, IIPs: idiopathic interstitial pneumonias, IP: interstitial pneumonia, **MPA:** microscopic polyangiitis, **MPO:** myeloperoxidaseMPO-ANCA positive interstitial pneumonia

based on the epidemiological evidence to date. There are ethnic differences in the prevalence of AAV, with GPA and proteinase 3 (PR-3)-ANCA positive AAV accounting for the majority of AAV in European populations by clinical classification and ANCA specificity, respectively, whereas MPA and MPO-ANCA positive AAV dominate in East Asian populations, including the Japanese (48-50). It is also important to recognize ethnic differences when considering MPO-ANCA positive interstitial pneumonia. To promote epidemiological studies aimed at building an international consensus on MPO-ANCA positive interstitial pneumonia in terms of pathophysiology, diagnosis and standard treatment strategies, it is essential that the pulmonologist and rheumatologist continue to work closely together.

Conflicts of interest: Each author declares that he or she has no commercial associations (e.g. consultancies, stock ownership, equity interest, patent/licensing arrangement etc.) that might pose a conflict of interest in connection with the submitted article.

Legends: AAV: ANCA-associated vasculitis, ANCA: anti-neutrophil cytoplasmic antibody, IIPs: idiopathic interstitial pneumonias, IP: interstitial pneumonia, MPA: microscopic polyangiitis, MPO: myeloperoxidase.

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