Interstitial lung disease in microscopic polyangiitis and granulomatosis with polyangiitis: demographic, clinical, serological and radiological features of an Italian cohort from the Italian Society for Rheumatology

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Abstract

Objective

Interstitial lung disease (ILD) has been described as a possible pulmonary involvement in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV), mainly granulomatosis with polyangiitis (GPA) and microscopic polyangiitis (MPA). The aim of this cross-sectional Italian national study was to describe demographic, clinical and serological profile of ILD related to MPA and GPA and investigate possible correlations between radiologic patterns of ILD and vasculitis features.

Methods

We enrolled 95 consecutive patients with AAV-ILD, 56 affected by MPA (58.9%) and 39 by GPA (41.1%).

Results

NSIP was the most frequently detected ILD pattern, observed in c-ANCA patients in 60.9% of cases, followed by UIP pattern mainly observed in p-ANCA patients (47.7%, p=0.03). ILD represented the first clinical manifestation, preceding vasculitis diagnosis in 22.1% of cases and, globally, ILD was already detectable at AAV diagnosis in 66.3% of patients. The diagnosis of ILD preceded that of AAV in 85.7% of p-ANCA positive-patients, while only one patient with c-ANCA developed ILD before AAV (p=0.039). Multivariate analysis confirmed the correlation of UIP pattern with p-ANCA-positivity and a diagnosis of ILD before AAV, also when adjusted for age and sex.

Conclusion

Our study confirms that UIP is a frequent pattern of lung disease in AAVILD patients. Our results also suggest that ILD can represent an early complication of AAV but also occur in the course of the disease, suggesting the need of a careful evaluation by both pulmonologist and rheumatologist to achieve an early diagnosis. Further prospective studies are needed to define ILD prevalence and evolution in AAV patients.

Key words

interstitial lung disease, ANCA-associated vasculitides, granulomatosis with polyangiitis, microscopic polyangiitis, usual interstitial pneumonia

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Introduction

Antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitides (AAV) are a heterogeneous group of vasculitis affecting small vessels. They are represented by granulomatosis with polyangiitis (GPA, formerly Wegener's granulomatosis), microscopic polyangiitis (MPA), together with renal-limited vasculitis, and eosinophilic granulomatosis with polyangiitis (EGPA, formerly Churg Strauss disease) (1, 2).

Myeloperoxidase (MPO) and proteinase-3 (PR3) represent the target of ANCA (MPO-ANCA and PR3-ANCA respectively). The former is more frequent in MPA and EGPA patients, the latter can be found in about 80% of patients with GPA. However, these ANCA specificities are not pathognomonic for different AAV and the negativity of ANCA does not exclude a diagnosis of AAV. Diagnosis is generally defined in presence of a combination of clinical and serological findings and/or histological evidence of necrotising pauci-immune small-vessel vasculitis (1, 3-6).

Different types of pulmonary involvement have been described in AAV patients; however, the association with interstitial lung disease (ILD) has been also described, mainly in MPA and GPA patients (7, 8). ILD is a rare condition that is well defined in its idiopathic forms, such as idiopathic pulmonary fibrosis (IPF), but also recognised as a frequent complication occurring in immune-mediated rheumatic diseases, such as systemic sclerosis, rheumatoid arthritis, idiopathic inflammatory myopathies, and Sjögren's syndrome (9-11). Our knowledge about ILD in course of AAV is mainly derived from case series, showing that ILD frequently occurs in elderly patients with detectable circulating MPO-ANCA, with usual interstitial pneumonia (UIP) being the most frequent pattern at high-resolution computed tomography (HRCT). Interestingly, in a percentage of patients, the diagnosis of ILD preceded that of AAV (8).

The aim of our cross-sectional multicentric Italian national study was to describe the demographic, clinical and serological profile of ILD secondary to MPA and GPA and investigate possible correlations between HRCT patterns and vasculitis features.

Patients and methods

Diagnosis of AAV

In this national multicentre cross-sectional study, we enrolled all consecutive patients with a diagnosis of ILD associated to confirmed MPA or GPA attending the Rheumatology Units of 14 Italian Centres for a 6-month period (from July 1, 2019 to December 31, 2019).

Diagnosis of GPA or MPA was made on the basis of current classification criteria (12-15), or by expert rheumatologists according to clinical presentation, laboratory and imaging finding (16). Classification of enrolled AAV patients was revised after the publication of new 2022 American College of Rheumatology/European Alliance of Associations for Rheumatology Classification Criteria for MPA and GPA (17, 18).

The serum ANCA positivity was tested on ethanol-fixed neutrophils by indirect immuno-fluorescence (IIF), and/or with a standard commercial enzyme-linked immunosorbent assays (ELISA) to detect specific antibodies directed against PR3 or MPO, according to the practice of each immunology laboratory (19).

In particular, all patients underwent IIF, and all patients but 3 underwent ELISA (2 patients were negative at IIF and 1 patient was p-ANCA positive at IIF).

ILD assessment

The diagnosis of ILD was made by means of chest HRCT and multidisciplinary discussion involving at least rheumatologist, pulmonologist and radiologist. Other possible causes of ILD, different from AAV, were excluded. The last available HRCT at the moment of enrolment was considered to determine the radiological pattern. For each centre, HRCT scans were re-assessed by an expert chest radiologist who interpreted the radiologic pattern of ILD according to the Fleischner Society White Paper statement on the diagnosis of idiopathic pulmonary fibrosis (IPF) (20). The pattern of disease was recorded as definite, probable UIP or indeterminate for UIP. If a pat-

tern indeterminate for UIP was noted, it was further classified as nonspecific interstitial pneumonia (NSIP), organising pneumonia (OP) or other patterns, that can also be observed in combination (20-22).

The last available HRCT and pulmonary function tests (PFTs), if available, were recorded.

PFTs were performed in all centres according to standard methods (23, 24). The results of PFTs were expressed as percentage of the predicted value of each parameter and corrected for age, gender and height. Pulmonary function was evaluated by means of forced vital capacity (FVC). Single-breath diffusing capacity of the lung for carbon monoxide (DLCO-SB) was used to assess gas transfer.

Vasculitis assessment

For all patients, demographic data, clinical and serological characteristics of vasculitis, time of diagnosis of MPA or GPA and ILD, as well as the presence of pulmonary symptoms such as dry cough and dyspnoea were recorded at the time of vasculitis or ILD diagnosis. Past and current treatments for each patient were also collected. All data were recorded on a standardised case-report form and entered into a computerised database.

Disease activity was determined using the Birmingham Vasculitis Activity Score (BVAS), version 3 (25).

Ethics

The study was approved by the local Institutional Review Board "Comitato Etico Area Vasta Nord" (approval number: AOU0011234/20).

Statistical analysis

Statistical analysis was performed using STATA® software v. 14 (StataCorp. 2015. Stata Statistical Software: Release 14. College Station, TX: StataCorp LP.). Descriptive statistics were presented for baseline demographic clinical characteristics for the entire group, as well as for the groups of patients. Continuous variables were presented as the number of patients (N), median and interquartile range (IQR), and compared between subgroups using non-

Table I. Demographic, clinical and serological features of patients.

		n	%
Total number	95		
GPA/MPA	39/56	41/59	
Ever smokers	28	29.5	
Male/Female ratio		52/43	54.7/45.3
pANCA	65	68.4	
cANCA	23	24.2	
Anti-MPO	52	54.7	
Anti-PR3	21	22.1	
ILD pattern			
	UIP	36	37.9
	NSIP	49	51.6
	OP	10	10.5
ILD occurrence			
	Concurrent	42	44.2
	Preceding	21	22.1
	Following	32	33.7
ILD occurrence			
	Until 6 months*	63	66.3
	More than 6 months*	32	33.7
First clinical manifestation of vasculitis (more results possible)			
	Skin vasculitis	9	9.5
	Renal involvement	34	35.8
	Neurological involvement	15	15.8
	ENT involvement	18	18.9
	Lung involvement	60	63.2
	Other	25	26.3
Clinical manifestations of vasculitis			
	Skin vasculitis	20	21.1
	Renal involvement	49	51.6
	Neurological involvement	37	40.6
	ENT involvement	36	37.9
	Arthritis	29	30.5
Lung involvement			
	Asthma	4	4.2
	Alveolar haemorrhage	13	13.7
	Lung cavitation	11	11.6
	Lung infiltrates	35	36.8
	Serositis	13	13.7
	ARDS	14	14.7
Cough		35	36.8
Dyspnoea		55	57.9
		Median	**IQR**
Median age years (IQR)		69	62, 75
Median disease duration months (IQR)		31	8, 74
Median interval vasculitis-ILD onset months (IQR)		0	-12, 16
B-VAS diagnosis		14	8, 20
B-VAS enrolment		1	0, 5
FVC % (IQR)		85	70, 101
DLCO % (IQR)		57	44, 77
Treatments		**n**	**%**
Cyclophosphamide		48	50.5
Rituximab		44	46.3
Mycophenolate mofetil		24	25.3
Azathioprine		38	40
Methotrexate		18	18.9
Glucocorticoids		93	97.9

*since the diagnosis of AAV.

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase-3; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; ENT: ear, nose and throat ; ARDS: Acute Respiratory Distress Syndrome; B-VAS: Birmingham Vasculitis Activity Score; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide.

parametric Mann-Whitney test; while categorical variables were presented as frequency (n, percentage [%]) and compared using Pearson's chi-squared test or Fisher's exact test as appropriate. The association between these parameters and UIP versus other patterns was assessed using a logistic regression model with stepwise forward selection. In the first step, the intercept-only model was fitted and individual score statistics for the potential variables were evaluated. A significance level of $p<0.05$ was used to allow a variable into the model. In stepwise selection, an attempt was made to remove any insignificant variables from the model before adding a significant variable to the model. The Hosmer and Lemeshow test was used to evaluate "goodness of fit" in the selection model. Data from the univariate and multivariate logistic regression analyses were expressed as odds ratio (OR) and 95% confidence interval (CI). A *p*-value <.05 was considered statistically significant.

Results

Characteristics of AAV-ILD patients

A total of 95 patients were enrolled, 56 affected by MPA (58.9%) and 39 by GPA (41.1%). Fifty-two patients were males (54.7%) and 43 females (45.3%), a median age of 69 years (62, 75), and the median disease duration of AAV was of 31 months (8, 74). P-ANCA positivity was detected in 65 patients (68.4%), c-ANCA in 23 patients (24.2%). MPO-ANCA were detected in 52 patients (54.7%), while PR3-ANCA were observed in 21 patients (22.1%). Among HRCT patterns, a UIP, NSIP, or other patterns, were observed in 36, 49 and 10 patients (37.9, 51.6, 10.5% respectively).

Details about demographic, serological and clinical features of AAV-ILD patients are summarised in Table I.

Comparison between p-ANCA and c-ANCA patients

Our population enclosed 65 patients with p-ANCA (31 females and 34 males respectively) and 23 patients with c-ANCA positivity (7 females and 16 males respectively), see Table II for more details.

Table II. Demographic, clinical and serological features of patients with pANCA and cANCA.

	pANCA n (%)	cANCA n (%)	*p*
Total number	65 (68.4)	23 (24.2)	
Male/Female ratio	34/31	16/7	0.13
ILD pattern			
UIP	31 (47.7)	4 (17.4)	
NSIP	29 (44.6)	14 (60.9)	0.03
Other	5 (7.7)	5 (21.7)	
ILD occurrence			
Following	18 (27.7)	10 (47.8)	
Concurrent	29 (44.6)	11 (47.8)	0.13
Preceding	18 (27.7)	1 (4.3)	
Median age years (IQR)	69.5 (63, 75)	66 (59.5, 74.5)	0.07
Median disease duration months (IQR)	25 (8, 71)	27.5 (4, 133)	0.46
Median interval vasculitis-ILD onset months (IQR)	-2.5 (-14.5, 2.5)	60 (0, 113)	<0.01
B-VAS diagnosis (IQR)	16 (10, 21)	17 (7, 21)	0.42
B-VAS enrolment (IQR)	0 (0, 5)	2 (0, 5)	0.47
FVC % (IQR)	86 (70.5, 101.5)	81 (72.5, 103,5)	0.65
DLCO % (IQR)	56.5 (46, 74)	66 (53.5, 88.5)	0.18

ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; OP: organising pneumonia; B-VAS: Birmingham Vasculitis Activity Score; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide.

Table III. Characterisation of ANCA-negative patients with AAV and ILD.

Case	Diagnosis	Clinical picture at diagnosis
1. Female, 66	GPA	lung nodules, peripheral neuropathy, cardiac involvement, ENT involvement*
2. Male, 75	GPA	lung nodules and cavitations, glomerulonephritis**, purpura, chronic sinusitis, ENT involvement*
3. Female, 59	GPA	lung nodules and infiltrates, ENT involvement, arthritis, constitutional symptoms
4. Female, 59	GPA	lung involvement with infiltrates and respiratory failure (ARDS), peripheral neuropathy, CNS involvement, chronic sinusitis, ENT involvement*
5. Female, 57	GPA	middle ear involvement**, mononeuritis multiplex, arthritis, CNS involvement
6. Female, 53	GPA	multiple mononeuritis**, arthritis, central nervous system involvement
7. Male, 73	MPA	skin vasculitis**, transient lung infiltrates, peripheral neuropathy, constitutional symptoms

*Ear, nose, throat, including otitis media, bloody nasal discharge and crusting.
**confirmed by biopsy.
GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; ENT: ear, nose and throat; ARDS: Acute Respiratory Distress Syndrome.

ANCA were negative in 7 patients. No differences were observed with regard to median age at diagnosis and disease duration of vasculitis, while a short disease duration between AAV and ILD diagnosis was observed in p-ANCA patients ($p<0.01$). UIP pattern was more frequent in p-ANCA than in c-ANCA patients (47.7%), while NSIP pattern was detected in 60.9% of c-ANCA patients, with a statistically significant difference ($p=0.03$).

Six out of seven (85.7%) ANCA negative patients showed an NSIP pattern, and ILD diagnosis followed AAV diagnosis in 3/7 cases (42.8%). General features of ANCA negative patients are summarised in Table III.

All 7 patients had a diagnosis of ANCA negative vasculitis according to the

opinion of a rheumatologist expert in vasculitis and satisfied the new ACR/EULAR AAV classification criteria (17, 18). Furthermore, the diagnosis of vasculitis was confirmed by biopsy in 4 patients and histology was compatible with 2012 Revised International Chapel Hill Consensus Conference Nomenclature (CHCC) for MPA or GPA (14). All 7 patients had long-term follow-up and other diagnoses were excluded.

Comparison according to temporal correlation between ILD and AAV diagnosis

ILD was diagnosed before AAV in 21 patients (22.1%), the diagnoses of ILD and AAV were concomitant in 42 patients (44.2%), while in 32 patients (33.7%) ILD followed the diagnosis of AAV.

P-ANCA positivity was observed in 18/21 patients (85.7%) in whom the diagnosis of ILD preceded that of AAV, while c-ANCA were detected only in 1 case. Evaluating ANCA specificities, we observed that PR3-ANCA were detected in patients with ILD preceding AAV only in one case (p=0.039).

Patients in whom ILD was detected before the diagnosis of AAV revealed mainly a UIP pattern (41.7%) while NSIP pattern occurred less frequently (10.2%). Regarding ILD occurrence in relation to the time of AAV diagnosis, the differences were statistically significant (p=0.003) (Table IV).

Comparison according to HRCT pattern of UIP or NSIP

NSIP pattern was detected in 49 patients (51.6%), 25 females and 24 males (51% and 49% respectively), while UIP pattern was detected in 36 patients (37.9%), 13 females and 23 males (36.1% and 63.9%, respectively).

UIP pattern was observed more frequently in patients with a diagnosis of MPA (27/56, 48.2%) while NSIP pattern was more frequent in GPA patients (30/39, 76.9%) (p=0.018). P-ANCA were more frequently observed in patients with UIP pattern compared to those with NSIP pattern (86.1% *versus* 59.2%, p<0.001), furthermore ever smoking was found to be significantly associated with UIP pattern (51.6% *versus* 25%, p=0.02), but no correlation was detected between smoking and ANCA pattern (p=0.79). No significant differences were observed in regard to MPO-ANCA and PR3-ANCA, median age at AAV diagnosis, vasculitis duration and interval between AAV and ILD diagnoses (Table V).

Table IV. Demographic, clinical and serological features of patients according to ILD onset.

	preceding n (%)	concurrent n (%)	following n (%)	*p*
Total number	21 (22.1)	42 (44.2)	32 (33.7)	
GPA/MPA	4/17	19/23	16/16	0.062
Male/Female ratio	14/7	20/22	18/14	0.351
pANCA	18 (85.7)	29 (69)	18 (56.3)	
cANCA	1 (4.8)	11 (26.2)	11 (34.4)	0.13
ANCA-negative	2 (9.5)	2 (4.8)	3 (9.4)	
Anti-MPO	13 (61.9)	25 (59.5)	14 (48.3)	0.548
Anti-PR3	1 (4.8)	14 (33.3)	6 (20.7)	0.037
ILD pattern				
UIP	15 (71.4)	10 (23.8)	11 (34.4)	
NSIP	5 (23.8)	25 (59.5)	19 (59.4)	0.011
Other	1 (4.8)	7 (16.7)	2 (6.2)	
Median age years (IQR)	70 (66, 74)	65 (62, 75)	69 (55, 75)	0.074
Median disease duration months (IQR)	32 (5.5, 70.5)	12 (6, 56)	52 (24, 137)	0.025
Median interval vasculitis-ILD onset months (IQR)	-22 (-65, -12)	0 (-3, 0)	47 (15, 118)	<0.001
B-VAS diagnosis (IQR)	13 (7, 17)	15.5 (11, 21)	15 (9, 23)	0.25
B-VAS enrolment (IQR)	1 (0, 3)	0 (0, 4)	2 (0, 8)	0.1
FVC % (IQR)	75 (64, 101)	98 (78, 112)	78 (69, 93)	0.076
DLCO % (IQR)	47 (34, 71)	64 (51, 89)	61 (52, 74)	0.173

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase-3; ILD: interstitial lung disease; UIP: usual interstitial pneumonia; NSIP: nonspecific interstitial pneumonia; B-VAS: Birmingham Vasculitis Activity Score; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide.

Table V. Demographic, clinical and serological features of patients according to the radiological pattern.

	UIP	NSIP	*p*
Total number	36 (37.9)	49 (51.6)	
GPA/MPA	9/27	30/29	0.018
Male/Female ratio	23/13	24/25	0.172
Ever smokers	16 (51.6)	10 (25)	0.021
pANCA	31 (86.1)	29 (59.2)	<0.001
cANCA	4 (11.1)	14 (28.6)	0.06
Anti-MPO	24 (66.7)	24 (51.1)	0.154
Anti-PR3	6 (16.7)	11 (23.4)	0.451
ILD occurrence			
Preceding	15 (41.7)	6 (10.2)	
Concurrent	10 (27.8)	25 (51)	0.003
Following	11 (30.6)	19 (38.8)	
ILD occurrence			
Until 6 months	25 (69.4)	38 (64.4)	0.66
More than 6 months	11 (30.6)	21 (35.6)	
Median age years (IQR)	69.5 (63, 75)	69 (62, 75)	0.21
Median disease duration months (IQR)	23 (6, 63)	52.5 (11, 97)	0.83
Median interval vasculitis-ILD onset months (IQR)	-3 (-24, 13)	0 (-5, 96)	0.393
B-VAS diagnosis	14.5 (10.5, 21.5)	16 (8, 20)	0.59
B-VAS enrolment	1 (0, 9)	1 (0, 3)	0.48
FVC % (IQR)	86 (68, 101)	83.5 (69, 100)	0.921
DLCO % (IQR)	60 (44, 77)	56.5 (46, 73)	0.882

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; ANCA: antineutrophil cytoplasmic antibodies; MPO: myeloperoxidase; PR3: proteinase-3; ILD: interstitial lung disease; B-VAS: Birmingham Vasculitis Activity Score; FVC: forced vital capacity; DLCO: diffusing capacity of the lung for carbon monoxide.

Table VI. Multivariate analysis: factors associated to UIP pattern in AAV-ILD patients.

Parameter	Standard error	OD	95% CI	*p*
ANCA (p-ANCA)	3.13	4.4	1.10-17.73	0.04
Smoke	1.34	2.13	0.62-7.32	0.23
Occurrence before AAV (preceding)	5.23	7.6	1.97-29.31	<0.01
Male sex	1.14	1.79	0.51-6.22	0.36
Age	0.02	1.01	0.96-1.06	0.76

OR: odds ratio; CI: confidence interval; ANCA: antineutrophil cytoplasmic antibodies; AAV: ANCA-associated vasculitis.

Clinical and organ involvement, namely skin vasculitis, arthritis, renal, neurological and ENT involvement didn't correlate with HRCT pattern of ILD, neither with ANCA serology or time of ILD appearance (data not showed).

Multivariate analysis

Univariate analysis was performed to evaluate possible correlations between HRCT UIP pattern and AAV clinical-serological features, showing a significant association with MPA, smoke, p-ANCA and occurrence of ILD before AAV diagnosis. On the basis of the these results a multivariate regression model was also performed.

Therefore, the model included type of ANCA, smoking, and timing of ILD occurrence in comparison to vasculitis diagnosis. The analysis confirmed the correlation of UIP pattern with p-ANCA (OR 4.40; 95%CI: 1.10–17.72) and ILD diagnosed before AAV appearance (OR 7.60; 95%CI 1.97–29.31), also when adjusted for age and sex (Table VI).

Discussion

In this paper, we investigated for the first time in a cross-sectional study in an Italian population, the serological, clinical and radiological features of ILD associated to MPA and GPA patients.

Our results showed that NSIP was the HRCT ILD pattern most frequently detected in AAV patients, and the diagnosis of ILD was predominantly made before or concurrently with that of vasculitis. Moreover, UIP pattern was more frequently observed in p-ANCA positive patients.

During the last few years, an increasing number of publications reported the association between ILD and AAV. In 2014, Comarmond *et al*. described a population of 49 patients with ILD associated with AAV. The diagnosis of ILD preceded the diagnosis of vasculitis in 45% of patients, was concurrent in 43% and followed the diagnosis of AAV in 12% of patients. In 88% of cases, ANCA were MPO. In regard to radiologic pattern, UIP was the most frequently detected (43%), while other patterns were: atypical UIP (14%), fibrotic NSIP (7%), combined pulmonary fibrosis and emphysema (CPFE) (21.4%), NSIP (9.5%), and finally indeterminate (neither UIP nor NSIP although reticulation was present) in the remaining patients (4.8%) (26).

Recently, a larger AAV-ILD cohort was described by Maillet *et al*. including 62 AAV-ILD patients, namely 53 MPA and 9 GPA. Also, in this case, ILD was diagnosed mostly before (52%) or simultaneously (39%) compared to the vasculitis diagnosis. The majority of patients (63%) showed a UIP pattern, while only 24 patients have a NSIP pattern (35%) (27). These authors also compared AAV-ILD to AAV patients without ILD observing that the former had a lower prevalence of systemic manifestations. Finally, patients with UIP pattern showed a shorter survival at Cox regression analysis, suggesting that AAV-ILD cases had less active vasculitis but a higher risk of death because of UIP, which progressed independently of vasculitis (27).

To better investigate features of AAV-ILD we compared different subgroups, according to antibody profile, HRCT pattern of ILD, and chronological relationship with AAV. To our knowledge, the population described in our paper represents the largest in literature, and we confirmed in this population some results already shown by previous studies. We observed that ILD represented the first clinical manifestation, preceding the vasculitis diagnosis, in 22.1% of cases and that globally ILD was already detectable at AAV diagnosis in 66.3% of patients. The new classification criteria for MPA highlights the importance of ILD for diagnosis of MPA, but, when vasculitis is absent, diagnosis of AAV remains challenging. In a multicentre Italian-Spanish study, only 9/58 ILD-patients with anti-MPO antibodies developed an MPA in a 39-month period, while 4 patients developed other rheumatic diseases. This result confirms that anti-MPO antibodies are necessary, but not sufficient, to make a diagnosis of MPA in ILD patients.

Other authors reported the presence of ANCA in patients with IPF, with a prevalence up to 35% in the Japanese population (28-30). However, the occurrence of vasculitis, mainly MPA, has been described in a minority of these cases and only 7–23% of ANCA-positive subjects with a diagnosis of IPF subsequently developed a clinically overt vasculitis, mainly in patients with anti-MPO antibodies (28, 29). Our data confirm the association between p-ANCA and the development of vasculitis in patients with ILD, because only one c-ANCA patient developed ILD before the occurrence of AAV.

In 2015, IPAF classification criteria were proposed, in order to define patients with interstitial pneumonia and some clinical, serological or morphological characteristics suggestive of rheumatic disease, but not sufficient to make a definite diagnosis. One limitation of these classification criteria was the lack of ANCA antibodies in the serological domain. Therefore, patients with ANCA and ILD could not be classified as IPAF in any case (31).

Until now, only a few studies have evaluated the features of ILD in c-ANCA positive and ANCA-negative patients with MPA and GPA (32-37). Interestingly, although limited by the low number of patients, we observed that c-ANCA positive and ANCA negative patients (30 patients, 31.6% of population) showed similar features being prevalently characterised by NSIP pattern (20/30 patients, 66.7%) and preceding the diagnosis of vasculitis only in a minority of patients (3/30, 10%).

This subgroup of patients could also explain the high prevalence of NSIP HRCT pattern recorded in our study if compared with other studies. In fact, according to the currently published studies (27, 38), our data confirm that UIP is the prevalent pattern observed in p-ANCA positive patients (47.7%), but we also observed that NSIP is predominant in c-ANCA positive and ANCA negative cases.

These results suggest that we can probably distinguish two different clinical phenotypes. In the first, ILD usually precedes vasculitis, patients are more frequently p-ANCA positive and have a predominant UIP pattern at HRCT. A number of these patients are initially classified as IPF, and therefore they need a careful assessment by the pulmonologist of clinical manifestations and laboratory findings during their follow-up for an early and appropriate management and treatment of vasculitis. In addition, this subgroup of patients has a poor prognosis more related to ILD than to vasculitis, and, in analogy to IPF, anti-fibrotic agents might be useful (8, 39, 40). This clinical subgroup supports the biological hypothesis of a fibrosing effect of ANCA-MPO (41).

On the other hand, in the second phenotype, NSIP pattern is frequently detected concomitantly with diagnosis of AAV or in the course of the disease; these patients are more frequently c-ANCA positive or ANCA-negative suggesting the need for a regular assessment also for ILD in patients with AAV, particularly in those with GPA.

Our study has many limitations, but also some strengths. First, since data at disease onset and diagnosis were retrospectively collected, incomplete data sets may have influenced the findings. Other limitations include possible referral bias of cases; patients in this cohort may represent the those with more severe ILD, while asymptomatic or mildly symptomatic patients may have been less frequently identified and included in the study.

Finally, the lack of a central reading of the HRCTs could represent a bias in HRCT pattern definition, but on the other side all the participant centres had thoracic radiologists with high expertise in parenchymal lung diseases.

A strength of this study is the large number of consecutive cases which should provide a more reliable perspective of the spectrum of ILD in MPA and GPA than the previous smaller series. Furthermore, the patients were uniformly evaluated with a standardised data collection.

Further prospective studies with larger and homogeneous populations are needed to better define the ILD prevalence and evolution in AAV, its clinical phenotype and possibly the better therapeutic approach.

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Competing interests

A. Berti has served on advisory boards and has received lecturing fees from GSK, all unrealted to the present publication. A. Giollo has received speaker and consultancy fees from Galapagos, Novartis and Eli Lilly. C. Dejaco has received research grants from Abbvie, honoraria for consultancies and/or speaker's bureau from Abbvie, Pfizer, Lilly, Galapagos, Roche, Sanofi, Novartis and Janssen. R. Caporali has received consulting fees from Abbvie, BMS, Amgen, Celltrion, Lilly, Fresenius-Kabi, Galapagos, Janssen, MSD, Novartis, Pfizer and UCB.

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