

Original article

Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study

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Abstract

Objectives. ANCA-associated vasculitis and interstitial lung disease (ILD) are uncommon conditions. The occurrence of both diseases in the same patient is increasingly recognized. Our aim was to ascertain the characteristics and outcomes of patients with ILD and ANCA-associated vasculitis.

Methods. A retrospective observational cohort study was performed. Patients who presented to the Hammersmith Hospital, London, with ANCA-associated vasculitis [granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis (MPA) or Churg–Strauss syndrome] who also had ILD were included. Following hospital discharge, all patients were followed up in a multi-disciplinary vasculitis clinic. We recorded patient demographics, diagnostic tests, treatment, complications and mortality.

Results. ILD was observed in 2.7% ($n = 14$) of our patients with ANCA-associated vasculitis ($n = 510$); all had MPO-ANCA and a clinical diagnosis of MPA, giving a prevalence of 7.2% in patients with MPA ($n = 194$). There was no significant difference in survival between patients with MPA and ILD and those with MPA alone.

Conclusion. It is important that physicians are aware of this clinical association and the presence of ILD should be considered in all patients with ANCA-associated vasculitis, especially those with MPO-ANCA. The possibility that patients with ILD may subsequently develop features of systemic vasculitis should also be remembered.

Key words: Interstitial lung disease, Anti-neutrophil cytoplasmic antibody, Vasculitis, Microscopic polyangiitis, Mortality.

Introduction

The ANCA-associated vasculitides are characterized by pauci-immune necrotizing vasculitis of small blood vessels. They comprise three different clinical syndromes: granulomatosis with polyangiitis (Wegener's), microscopic polyangiitis (MPA) and Churg–Strauss syndrome (CSS). However, despite the common association with ANCA, these disease entities differ significantly in their clinical features and possibly in underlying pathophysiology.

The association between interstitial lung disease (ILD) and ANCA-associated vasculitis (AAV), particularly MPA,

has been described in a number of case reports and small series, frequently identified from cohorts of patients with ILD. The two conditions are uncommon; AAV has an incidence of ~10–25 per million in North America and Europe [1], while ILD is estimated to occur in 7.4–10.7 per 100 000 [2]. The association between ILD and AAV is therefore unlikely to be a coincidence. Little has been published about the incidence of patients with ILD in a cohort of patients with AAV, their defining characteristics and overall outcomes.

Interestingly, this association appears to be almost uniquely between ILD and MPA, and specifically with anti-MPO-ANCA, suggesting that the particular antibody or its evoked response is critical for development of ILD. It is important that in cases of ILD, vasculitis should be ruled out as an underlying disorder, in view of other potential organ involvement and possible therapeutic interventions. This approach is recommended by the International Consensus on Idiopathic Pulmonary Fibrosis (IPF) [2].

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We determined the clinical and immunological characteristics of patients at our hospital with AAV and ILD, their response to treatment and outcome. In view of increased reporting of this association, we reviewed the literature to determine more widely the incidence, clinical features and outcome of these patients.

Methods

Patients

We conducted a retrospective study of patients attending the renal vasculitis clinic at Hammersmith Hospital between 1974 and 2009. Case notes of patients were reviewed for clinical features consistent with ILD, either at presentation or developing during treatment. Patients with dyspnoea, fine crackles on auscultation of the chest and alveolar shadowing on the chest radiograph (not explained by fluid overload or infection) were studied. Further evidence of ILD was sought from results of high-resolution computerized tomography (HRCT) scan, lung function testing and histology obtained at lung biopsy or at post-mortem examination.

Fourteen patients were identified as having clinical features of ILD satisfying all of the following inclusion criteria:

- (i) Radiological evidence of ILD on HRCT, and/or lung function testing consistent with ILD, and/or a lung biopsy confirming ILD.
- (ii) The exclusion of another possible aetiological factor in the development of ILD.
- (iii) Classified as MPA using the Chapel Hill consensus criteria [3].

Pulmonary haemorrhage was diagnosed if there was consistent history with unexplained anaemia, and radiological evidence of pulmonary haemorrhage or elevated KCO (>150% predicted).

Data collection

Patient demographics (age, gender, race, smoking history, drug and environmental exposure), clinical course (time of onset and presenting features of ILD and AAV) and treatment were determined from the case notes. Where possible, HRCT and pulmonary function tests were performed on presentation in patients with ILD. The imaging was reviewed by a respiratory radiologist (N.S.) and deemed to be consistent with ILD. Some patients subsequently had a lung biopsy to confirm the underlying diagnosis. ANCA was assessed by IIF, while antigen specificity and antibody titres were measured by ELISA. The primary outcome studied was mortality.

Statistical analysis

Data are presented as medians and ranges. Kaplan–Meier analysis was used to obtain survival curves, with the log-rank test used to calculate significance.

Results

Demographics

Between 1974 and 2009, we treated 510 patients with systemic vasculitis. Of these, 194 had MPA (with 22 considered to have renal-limited vasculitis at presentation), and 14 patients were found to have ILD and MPA (2.7% of all AAV patients and 7.2% of those with MPA). These 14 patients comprised 10 men and 4 women with a mean age at presentation of 67.3 years (median 68.0, range 51.6–85.5 years). Thirteen patients were Caucasian and one was Indo-Asian. Two (14%) patients were smokers, 8 (57%) were ex-smokers and 4 (29%) were non-smokers (Table 1).

All of the 13 patients tested for ANCA were ANCA positive with a peri-nuclear staining pattern and anti-MPO reactivity. One patient (Patient 1) presented before routine ANCA testing, but had a clinical diagnosis of MPA. One additional patient in our vasculitis cohort with ILD was positive for ANCA with a cytoplasmic pattern and anti-proteinase (PR3) reactivity, but also had an anti-GBM antibody, so was not included in this series. Two other patients with MPA also had ILD, but one had some occupational exposure to asbestos and one had been prescribed MTX elsewhere, before recognition of ILD, and so both were excluded from further analysis.

Presentation

The commonest presenting feature was constitutional symptoms ($n=11$). A number presented with respiratory symptoms including a dry cough and progressive dyspnoea ($n=8$), while six patients had overt pulmonary haemorrhage (Table 1). Other clinical features included arthritis/arthralgia ($n=6$), scleritis ($n=4$), rash ($n=2$), aphthous ulcers ($n=1$) and peripheral neuropathy ($n=1$).

Two of the 14 patients presented with ILD 6 months and 3 years before AAV. Three patients presented with AAV before ILD with a mean interval of 9.7 years (median 3.0, range 2–24 years). Nine patients presented with features of ILD and AAV concurrently. Six of the 14 patients had a clinical diagnosis of pulmonary haemorrhage at presentation.

The diagnosis of ILD was based on a combination of lung function testing, lung histology and HRCT. Bronchoscopy was performed largely to exclude infection. No patient had a lymphocytic bronchoalveolar lavage. One patient had none of these investigations, but had a chest radiograph and clinical findings consistent with IPF (Patient 3). Investigations were limited as he died shortly after presentation, and no post-mortem was performed. One patient had only a lung biopsy (Patient 1), and one patient had a combination of lung histology and lung function testing (Patient 4). Seven patients did not have a lung biopsy but had convincing lung function measurements and cross-sectional imaging. Four patients had all these three investigations.

At presentation, mean forced expiratory volume in 1 s (FEV₁) ($n=11$) was 2.1 l (80% predicted), mean vital capacity (VC) was 3.8 l (70% predicted), mean FEV₁/VC ratio was 78% and mean peak expiratory flow (PEF) was

TABLE 1 Clinical characteristics of patients

Patient	Gender	Age	Smoker	Renal function on presentation, $\mu\text{mol/l}$	Renal biopsy	IAH	Presentation with ILD	Diagnosis of ILD	Treatment (a) Induction (b) Maintenance	Age at death, years	Complicating factors	Cause of death
1	M	60	Yes	824	FSNGN	Yes	Concurrent	Bx	(a) Pred + CYC	61	-	Respiratory failure
2	M	68	Ex	381	FSNGN	No	6 months pre-AAV diagnosis	CT	(a) Pred + CYC	68	Probable CMV pneumonitis	Respiratory failure
3	M	85	Ex	1042	None available	Yes	Concurrent	Bx	(a) Pred + CYC	85	Arrhythmias, renal failure	Multi-organ failure
4	M	60	Yes	500	None available	Yes	3 years pre-AAV diagnosis	PFT	(a) Pred + CYC + PEX	60	Bacterial pneumonia, DIC, renal failure	Multi-organ failure
5	M	61	No	545	FSNGN	Yes	Concurrent	Bx	(a) Pred + CYC	71	-	Not known
6	F	71	No	656	FSNGN	No	Concurrent	Bx	(b) Pred	71	-	Not known
7	M	67	Ex	1164	FSNGN	Yes	Concurrent	CT	(a) Pred + CYC + PEX	67	Previous thoracoplasty for TB, <i>Aspergillus</i> pneumonia, renal failure	Respiratory failure
8	M	69	Ex	1092	FSNGN	Yes	Concurrent	Bx	(a) Pred + CYC + PEX	69	Renal failure	Not known
9	F	52	Ex	136	FSNGN	No	24 years post-AAV diagnosis	LFT	(a) Pred	79	Cushing syndrome, ischaemic heart disease	Respiratory failure secondary to pneumonia
10	M	55	No	267	None available	No	7 years post-AAV diagnosis	PFT	(b) AZA	58	Recurrent pneumonia	Respiratory failure
11	F	68	Ex	161	None available	No	3 years post-AAV diagnosis	CT	(a) CYC + Methyl/Pred (b) MMF + Pred (a) Pred + CYC	NA	Osteoporosis and hypothyroidism	NA
12	M	66	Ex	260	FSNGN with scarring	No	Concurrent	PFT	(b) Pred + AZA (a) Pred + CYC	NA	Hypertension	NA
13	M	78	Ex	280	FSNGN	No	Concurrent	PFT	(b) Pred + AZA (a) Pred + CYC + Ritux	NA	Ischaemic heart disease, gout, cerebrovascular disease, mycetoma, repeated pneumonia	NA
14	F	78	No	85	FSNGN	No	Concurrent	CT	(a) Pred + CYC (b) AZA	NA	Osteoporosis	NA

Chest radiograph and clinical findings consistent with pulmonary fibrosis (+), M: male; f: female; AAV: ANCA-associated vasculitis; Pred: prednisolone; PEX: rituximab; Bx: biopsy; PFT: pulmonary function test; IAH: intra-alveolar haemorrhage; FSNGN: focal and segmental necrotizing GN; DIC: disseminated intravascular coagulation.

421 l/min (94% predicted). Six (60%) out of 10 patients (Patients 8–12 and 14) had lung restriction (VC < 80% predicted), while 3 (30%) out of 10 (Patients 4, 13 and 14) had co-existing airflow obstruction (reduced FEV₁/VC ratio and/or low PEF). Carbon monoxide transfer (TL_{CO}) was reduced in 5 (50%) out of 10 patients (Patients 6–10 and 14) in whom it was measured. Mean corrected gas transfer (KCO) (TL_{CO} divided by alveolar volume) was 1.7 (123% predicted), suggesting that fibrosis was relatively limited at baseline.

Cross-sectional imaging was obtained in a total of 11 patients (Fig. 1, Table 2). The distribution of interstitial changes was predominantly peripheral (n=8).

Fig. 1 HRCT scans of the chest demonstrating progression of severe honeycombing in a patient with MPO-ANCA-positive MPA and pulmonary fibrosis (Patient 13).

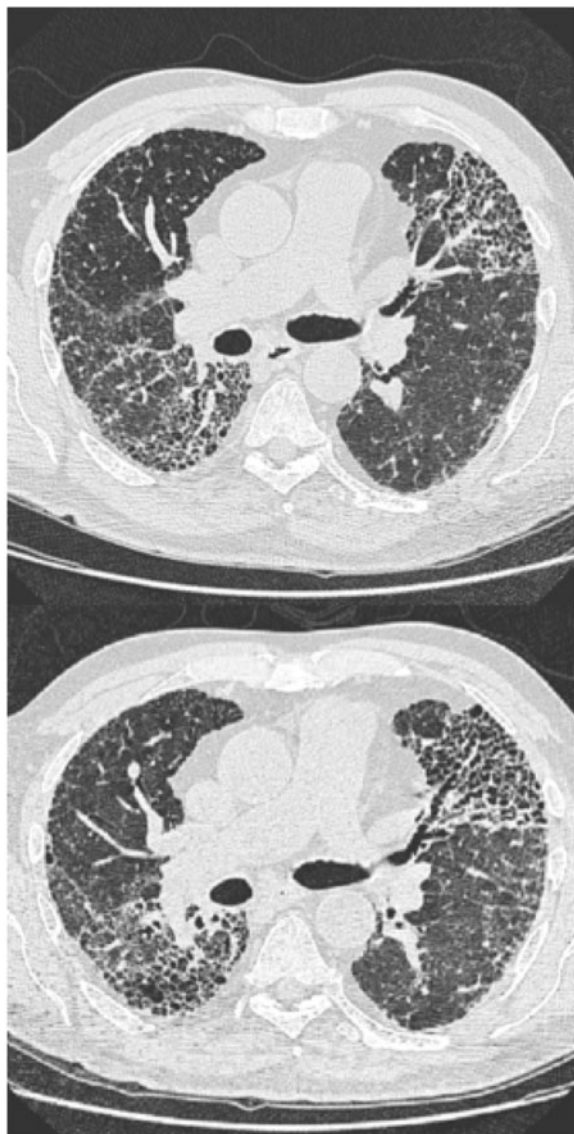


TABLE 2 Summary of radiological findings on CT thorax

Patient	Overall severity of lung change	Distribution—peripheral or central	Distribution—main location UZ, LZ	Symmetry	Cysts	Ground glass	Thickened inter-lobular septa	Emphysema	Traction	Progression
1	No imaging		LZ > UZ	+	++	+				
2	++	Peripheral	LZ > UZ	+	++	+++	+			
3	No imaging									
4	No imaging									
5	++	Peripheral	LZ > UZ	+	++	++	++		+	+
6	Minimal	Peripheral	LZ only	L > R	-	-				
7	Minimal	Peripheral	LZ only	R > L	-	+				
8	++	Central	LZ > UZ	+	++	++	++		+	+
9	+++	Both	LZ > UZ	+	+++	+	++		++	+
10	++++	Both	UZ = LZ	+	+++	+	++		++	+
11	+	Peripheral	LZ only	R > L	+	+	++		+	+
12	+++	Peripheral	LZ > UZ	+	+++	-	+		++	+
13	+++	Peripheral	LZ > UZ	+	+++	-	+		++	+
14	++	Peripheral	LZ > UZ	L > R	++	-			+	

LZ: lower zone; UZ: upper zone; L: left; R: right; -: absent; +: present on a scale of + to +++.

Two patients had both central and peripheral fibrosis, and one had a central distribution of fibrosis. Four patients had lower zone fibrosis only, while another six had predominantly lower zone fibrosis. One patient had equal distribution of fibrosis in the lower and upper zones. The distribution was symmetrical in seven patients, though four patients had a greater degree of fibrosis on either the left or right. Other findings included cysts ($n=9$), ground glass shadowing ($n=7$), thickened septa ($n=10$), emphysema ($n=4$) and traction ($n=7$).

The American Thoracic Society/European Respiratory Society International Multidisciplinary Consensus Classification of the Idiopathic Interstitial Pneumonias criteria were used to diagnose the pattern of ILD by CT criteria [4]. Eight patients were classified as having idiopathic pulmonary fibrosis/cryptogenic pulmonary fibrosis, two with desquamative interstitial pneumonia (DIP) and one with non-specific interstitial pneumonia (NSIP). Three patients did not have any cross-sectional imaging.

Mean serum creatinine on presentation was 528 mmol/l (median 441, range 85–1164 mmol/l). Ten of the 14 patients had a renal biopsy and all demonstrated a paucimmune focal necrotizing GN.

Treatment

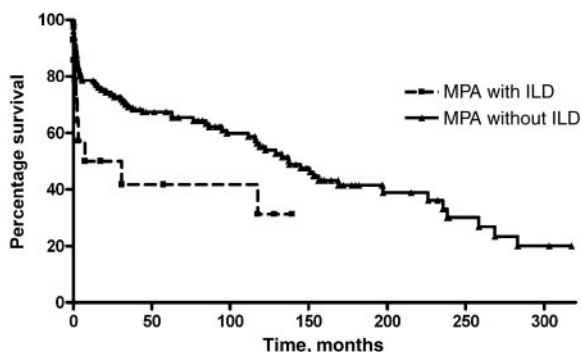
All but one patient received CYC and CSs as induction therapy (Table 1). The patient who did not receive CYC presented with mild disease and responded well to oral prednisolone (Patient 9). An additional three patients received plasma exchange and one patient received rituximab.

Among the nine patients who achieved remission, maintenance therapy was with AZA and steroids in four patients, while others were left on AZA alone ($n=2$), steroids alone ($n=1$) or steroids and MMF ($n=1$).

Outcome

We compared the outcome of patients with MPA and ILD ($n=14$) with that of patients with MPA without ILD ($n=180$) over the same time period (Fig. 2) and found no statistical

Fig. 2 Kaplan–Meier survival curve comparing the cohort of patients with MPA and ILD with those with MPA but without pulmonary ILD. There is no overall significant difference in survival between the groups ($P=0.07$).



difference in survival between these two groups ($P=0.07$), which should be treated with some caution due to the small cohort size. One- and five-year survival was 85 and 61% for the MPA patients without ILD, compared with 50 and 29% for those with ILD. We observed a higher mortality in patients with ILD presenting in the first two decades of our cohort (1976–96) compared with the later time period (1997–2008), primarily as a consequence of sepsis and the presence of pulmonary haemorrhage, in six out of nine patients who presented early in our series. These data explain the poor 1- and 5-year survival rates for those with ILD and MPA.

Mean time from presentation to death was 4.2 years (median 1.2, range 0.0–27.8 years). Mean follow-up for those who remained alive ($n=4$) was 7.5 years (median 8.0, range 1.7–12 years). Overall, the causes of death were respiratory failure (with or without superimposed pneumonia) in five cases, multi-organ failure/generalized sepsis in three cases and unknown in two cases.

After a mean of 5.1 years, mean FEV₁ ($n=11$) was 1.5 l (68% predicted) and VC 3.0 l (54% predicted). This represented a 29% reduction in FEV₁ and a 23% decrease in VC. Over the same period, TL_{CO} fell by 46% ($n=8$). However, there was considerable inter-individual variation in disease course. In one patient, there was an inexorable decline in lung function over 2.8 years (Patient 13). Serial HRCT scans revealed progression of ILD (Fig. 1). Lung function improved in two patients, with a mean increase in VC of 0.35 l (32% over baseline at presentation) up to 2.5 years follow-up (Patients 8 and 14).

Renal function generally improved following treatment. Mean serum creatinine of those achieving remission ($n=11$) was 232 μ mol/l (median 192, range 80–490 μ mol/l).

Discussion

In our experience, 2.7% of our patients with AAV had evidence of ILD, and all of them had a diagnosis of MPA, giving an incidence of 7.2% in this condition. The association between AAV and pulmonary fibrosis has been previously described in a number of reports totalling 99 patients (Table 3) [5–17]. The prevalence of ANCA in patients with ILD is suggested as 8–36% in the published literature [5, 10]. The prevalence of clinical ILD in AAV, however, has not been described.

The larger studies describing the association between AAV and ILD are from Japanese populations [10, 16, 17]. Interestingly, Japanese patients have a higher propensity to develop diffuse alveolar damage due to various aetiological factors, including drugs [18]. In addition, there is a predominance of MPA in Japan, with a high proportion of patients having MPO-ANCA, demonstrating differences in AAV demographics compared with predominantly white populations [19]. It is therefore possible that Japanese AAV patients, who are predominantly MPO-ANCA positive, are more prone to develop ILD.

It remains possible that the concurrence of AAV and ILD could be due to a common aetiological factor (e.g. silica) [20]. In an outpatient cohort, anyone with a history of exposure to a specific environmental factor that could have

TABLE 3 Literature review

Series	n	Age, years	Gender, %	AAV diagnosis, %	Time course, %	Deaths, %	Follow-up, months	ANCA specificity, %
Homma ^a [17]	31	Mean: 69	M: 55 F: 45	MPA: 26 SS: 13 PSS: 10 RA: 6 Others: 16 Unknown: 29	PF preceding AAV: 100	42	120	MPO: 100
Nozu ^b [10]	19	Median: 69 (52–89)	M: 37 F: 63	MPA: 21	PF preceding AAV: 100	35	90	MPO: 89 PR3: 11
Foulon ^c [5]	17	Mean: 66 (±11)	M: 88 F: 12	MPA: 41	PF preceding AAV: 76 PF concurrent with AAV: 24	59	57 (±41)	MPO: 29 Lactoferrin: 6 Unknown: 6 MPO: 100
Hervier [6]	12	Mean: 70.7 (64–78)	M: 75 F: 25	MPA = 83 WG = 17	PF concurrent with AAV: 67 PF preceding AAV: 12 AAV preceding PF: 8 PF preceding AAV: 100	58	49.2 (7–116)	MPO: 100
Eschun [8]	6	Mean: 70 (63–78)	M: 50 F: 50	MPA: 100	PF preceding AAV: 100	83	36	MPO: 100
Hiromura [16]	4	Mean: 67	M: 50 F: 50	MPA: 100	PF preceding AAV: 100	75	Not stated	MPO: 100
Nada [7]	3	Mean: 73	M: 33 F: 67	MPA: 100	PF preceding AAV: 33 PF concurrent with AAV: 67 PF concurrent with AAV: 100	100	120	P-ANCA: 67
Gindre [14]	2	Mean: 50.5	M: 100	WG: 100	PF concurrent with AAV: 100	50	Not stated	C-ANCA: 50 Not tested: 50
Becker-Merok [9]	1	65	M	MPA	PF preceding AAV	0	12	MPO: 100
Gallagher [11]	1	Not stated	Not stated	MPA	PF preceding AAV	100	15	MPO: 100
Birnbaum [12]	1	77	F	MPA	PF preceding AAV	0	>12	MPO: 100
Mansi [13]	1	55	F	MPA	PF preceding AAV	0	Not stated	MPO: 100
Souid [15]	1	75	M	MPA	AAV preceding PF	100	4	MPO: 100

^aCohort of PF patients investigated for anti-MPO antibody. Twenty-six per cent of patients had MPA vasculitis. (Other diagnoses in left column.) All had MPO-specific ANCA and co-existing PF. ^bCohort of PF patients investigated for ANCA. Twenty-one per cent had MPA. The rest had ANCA but not AAV. ^cCohort of PF patients investigated for AAV. Forty-one per cent (*n* = 7) had MPA. Ten patients had no vasculitis at all. AAV: ANCA-associated vasculitis; WG: granulomatosis with polyangiitis (Wegener's); PF: pulmonary fibrosis; PSS: progressive systemic sclerosis; PR3: proteinase 3.

resulted in ILD (one patient exposed to asbestos and another who had taken MTX) was excluded.

CYC therapy may be a confounding factor since there have been case reports of CYC-induced pulmonary fibrosis [21, 22]. The incidence of CYC-induced interstitial pneumonia and fibrosis is thought to be <1%, and it is generally a late complication [22, 23]. However, in our patients with AAV, the diagnosis of ILD was often made before the use of CYC.

ILD can be hard to distinguish from vasculitic infiltrates on imaging at the time of diagnosis, and repeat imaging may therefore be required. Ando *et al.* [24] reported the CT findings in 51 patients with MPO-ANCA-related disease. Pulmonary parenchymal honeycombing (consistent with late-stage interstitial fibrosis) was seen in five (37%) patients, and tended to have an asymmetric distribution in the lower zones bilaterally in the peripheries. In four patients, new honeycombing was seen on 3- to 6-month follow-up scans, but not on the initial scan. These areas corresponded to initial areas of consolidation, suggesting that initial intra-alveolar haemorrhage may have resulted in interstitial fibrosis. However, it is unclear why the rate of progression of interstitial disease varies between patients and why severe fibrosis does not appear to be a universal consequence of intra-alveolar haemorrhage. The development of ILD in ANCA-associated vasculitis does not seem to be directly related to overt pulmonary haemorrhage in our patients as over half the group did not have a history of pulmonary haemorrhage. Furthermore, there is no literature describing pulmonary fibrosis following haemorrhage in the context of anti-GBM disease and finally, of the six patients with pulmonary haemorrhage, one had a diagnosis of ILD that preceded diagnosis of AAV by 3 years, while the remaining five had the diagnosis of ILD made at the time of AAV presentation. These data argue against pulmonary haemorrhage being aetiologically important in the development of ILD. However, it does remain possible that ongoing subclinical pulmonary capillaritis may predispose to pulmonary fibrosis.

Our literature search identified 99 reported cases of concurrent pulmonary fibrosis and AAV (Table 3). In the 99 patients reported with AAV and ILD, the mean time to death was 3.5 years (median 5.3, range 0.08–13.7 years). This compares with a mean length of survival of ~2.3 years from the start of symptoms in ILD [25]. However, the mortality of ILD associated with AAV appears to be higher than that of AAV alone (cumulative patient 1- and 5-year survival of 82 and 76%, respectively) [26]. The 1- and 5-year survival of our patients with MPA vasculitis and ILD was 50 and 29%, respectively. This is much lower than expected for patients with MPA, who have 1- and 5-year survival of 85 and 61%. This may be as a result of the high mortality seen in our patients with severe vasculitis who presented before 1995. Of the five patients who presented after 1995, only one patient has died after 2.7 years. The other four patients are alive with follow-up between 1.7 and 12.3 years.

The cause of death in the 99 patients was primarily due to ILD and/or respiratory failure in 20 (41.7%). In our

experience, and that of others, interstitial fibrosis often appears to be generally progressive despite clinically quiescent systemic vasculitis. Lung function can conveniently be used to monitor progression.

We have not demonstrated any difference in mortality between patients with MPA vasculitis and co-existing ILD and patients with MPA vasculitis alone. This may be as a result of the relatively small number of patients included. To our knowledge, this is the first series to compare patients with MPA vasculitis and co-existing ILD with patients with MPA vasculitis without ILD. In one series, the mortality of MPO-ANCA-positive patients with ILD was greater than that of patients with ILD [17]. However, others have found no difference in long-term mortality between ANCA-positive and ANCA-negative patients with ILD [5, 6].

As expected, both serum creatinine of >500 $\mu\text{mol/l}$ ($P=0.0119$) and pulmonary haemorrhage at presentation ($P=0.0241$) predicted mortality at 5 years. Seven of 14 patients had a creatinine of <500 $\mu\text{mol/l}$ at presentation, none of whom had pulmonary haemorrhage. Seven of 14 patients had a creatinine of >500 $\mu\text{mol/l}$ at presentation, all but one of whom had pulmonary haemorrhage. Patients with a serum creatinine at presentation of >500 $\mu\text{mol/l}$ were much more likely to have pulmonary haemorrhage and vice versa ($P=0.0047$).

Patients with a serum creatinine of >500 $\mu\text{mol/l}$ at presentation and pulmonary haemorrhage (i.e. more severe vasculitis) were more likely to die at 5 years ($P=0.0225$). Coincidentally, among our cohort of patients, those presenting before 1995 were more likely to present with both pulmonary haemorrhage and a serum creatinine of >500 $\mu\text{mol/l}$ ($P=0.031$). This probably accounts for our observation that mortality was greater in patients presenting before 1995 ($P=0.0375$) as a result of more severe disease. Routine ANCA testing may have facilitated earlier diagnosis and referral, which in turn may have reduced the morbidity and mortality of ANCA vasculitis.

The main limitation of this study is its retrospective nature. As a consequence, there are some missing data such as lung function results. Furthermore, not all our patients with ANCA-associated vasculitis have been screened for ILD. As a result, there may be subclinical ILD in a number of our patients, introducing a selection bias.

The association between MPO-ANCA and ILD is striking. All 97 patients described in the literature tested for ANCA were positive; 94% demonstrating a P-ANCA pattern, and 85% specificity for MPO-ANCA. This raises a possible aetiological role for MPO-ANCA in ILD. Cambridge *et al.* [27] have reported an association between MPO-ANCA and ILD in patients with RA. There appears to be a pathogenic role for MPO-ANCA in pulmonary injury as demonstrated *in vivo* using rodents immunized with human MPO, or injected with anti-MPO antibodies [28, 29]. Further investigation of the role of MPO-ANCA in the pathogenesis of ILD is required.

Awareness of the association between AAV and ILD should enable us to determine its true incidence and

response to treatment. It may be prudent to monitor ANCA titres in patients with ILD who may subsequently develop features of systemic vasculitis. Similarly, ILD may develop in patients with MPA vasculitis. Although there is no specific treatment for this patient cohort at present, pulmonary disease seems to be progressive and morbidity and mortality often relate to the underlying pulmonary fibrosis. Thus, monitoring of lung function is important.

Rheumatology key messages

- There is a striking association between MPO-ANCA, MPA and ILD.
- Pulmonary fibrosis can be progressive despite clinically quiescent systemic vasculitis.
- ILD may be progressive, contributes to morbidity and mortality and exhibits inter-individual variation.

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