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Original article

Pulmonary involvement in primary systemic vasculitides

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Abstract

Objectives. This study describes the spectrum and initial impact of pulmonary manifestations in the primary systemic vasculitides.

Methods. Description and comparison of pulmonary manifestations in adults with Takayasu's arteritis (TAK), GCA, granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA), eosinophilic GPA (EGPA), polyarteritis nodosa (PAN) and IgA vasculitis (IgAV), using data collected within the Diagnostic and Classification Criteria in Vasculitis study.

Results. Data from 1952 patients with primary vasculitides were included: 170 TAK, 657 GCA, 555 GPA, 223 MPA, 146 EGPA, 153 IgAV and 48 PAN. Pulmonary manifestations were observed in patients with TAK (21.8%), GCA (15.8%), GPA (64.5%), MPA (65.9%), EGPA (89.0%), PAN (27.1%) and IgAV (5.9%). Dyspnoea occurred in patients with TAK (14.7%), GCA (7.8%), GPA (41.8%), MPA (43.5%), EGPA (65.8%), PAN (18.8%) and IgAV (2.6%). Cough was reported in TAK (7.6%), GCA (9.3%), GPA (34.8%), MPA (37.7%), EGPA (55.5%), PAN (16.7%) and IgAV (3.3%). Haemoptysis occurred mainly in patients with ANCA-associated vasculitis (AAV). Fibrosis on imaging at diagnosis was documented in GPA (1.9%), MPA (24.9%) and EGPA (6.3%). Only patients with AAV (GPA 2.7%, MPA 2.7% and EGPA 3.4%) required mechanical ventilation. At 6 months, the presence of at least one pulmonary item in the Vasculitis Damage Index was observed in TAK (4.1%), GCA (3.3%), GPA (15.4%), MPA (28.7%), EGPA (52.7%), PAN (6.2%) and IgAV (1.3%).

Conclusion. Pulmonary manifestations can occur in all primary systemic vasculitides, but are more frequent and more often associated with permanent damage in AAV.

Key words: vasculitis, ANCA-associated vasculitis, interstitial lung disease, pulmonary

CLINICAL SCIENCE

Rheumatology key messages

- Pulmonary involvement may occur in all primary systemic vasculitides.
- Pulmonary manifestations vary and may be useful to differentiate between different AAV.
- Pulmonary manifestations are more frequent and more often associated with permanent damage in AAV.

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Introduction

Pulmonary involvement in primary systemic vasculitides varies in its clinical presentation and frequency, depending on the type of vasculitis [1–3]. Because of the low prevalence of primary vasculitides, most information regarding pulmonary involvement comes from case reports or relatively small series.

Pulmonary manifestations have mainly been described in ANCA-associated vasculitides [AAV; granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic GPA (EGPA)]. Alveolar haemorrhage is frequent and can be seen in all AAV, although mostly in MPA. Patients with GPA can have pulmonary nodules, cavitating lesions, alveolar haemorrhage, endobronchial lesions or subglottic stenosis [4, 5]. Interstitial lung disease and pulmonary fibrosis is less frequent and mostly seen in MPA [6]. Adult-onset relapsing and/or refractory asthma is a hallmark of EGPA, but lung opacities with eosinophilia, nodules and alveolar haemorrhage have also been reported [7, 8].

Other small-, medium- and large-vessel vasculitides (LVVs) can also affect the lungs, pulmonary arteries and/or respiratory tract [3]. Takayasu's arteritis (TAK) is a large-vessel vasculitis affecting the aorta and its branches, and pulmonary artery involvement has been reported with various frequencies [9–11]. GCA predominantly affects elderly patients. Although incompletely understood, it is estimated that up to 10% of patients with GCA will have respiratory symptoms such as cough, sore throat, and/or hoarseness [12, 13]. Polyarteritis nodosa (PAN) does not typically involve the lungs. There have been a few reports describing the presence of diffuse alveolar haemorrhage in PAN, which was more likely among patients who would now be classified as having a diagnosis of MPA [14–17]. IgA vasculitis (IgAV) is a small-vessel vasculitis most often affecting young patients, in which diffuse alveolar haemorrhage has been occasionally reported [18–20].

The objective of this study was to describe pulmonary involvement at diagnosis across multiple vasculitides, analyse its severity and its short-term prognostic value, using a recent, large international database of patients with primary vasculitis.

Methods

Study design and population

The Diagnostic and Classification Criteria in Vasculitis Study (DCVAS), initiated in 2010, is a large international cohort of well-characterized patients with different vasculitides. The purpose of DCVAS was to develop and validate diagnostic and classification criteria for systemic vasculitis for use in daily clinical practice and in clinical trials. A detailed description of the DCVAS study has been previously published [21].

The present study analysed data from patients enrolled in DCVAS between 2010 and 2016 with a definitive diagnosis of TAK, GCA, GPA, MPA, EGPA, PAN or IgAV. Patients were enrolled within the first 24 months after diagnosis of vasculitis was made, with data entered referent to the time of diagnosis and 6 months later. To improve feasibility of recruitment, an exception was made for patients with TAK and PAN by allowing recruitment within 5 years of diagnosis. The final diagnosis and confidence in the diagnosis were determined at the time of inclusion and month 6 by the investigator. Only patients with the seven types of vasculitis outlined above and for whom the investigator was very certain of the diagnosis by month 6 were included in this analysis.

Clinical data elements

Data from the time of diagnosis were analysed for the patients' demographics, comorbidities, clinical manifestations and, when performed, results of pulmonary function tests [normal, restrictive or obstructive patterns, low diffusing capacity for carbon monoxide (DLCO)], lung imaging (chest radiograph, CT-scan or PET-CT study), bronchoscopy and lung biopsy. Laboratory test results included complete blood cell count, serum creatinine level and serum autoantibodies [ANCA, anti-glomerular basement membrane (anti-GBM), RF, anti-CCP antibodies and ANAs].

Data from the 6-month follow-up visits were also analysed including the Vasculitis Damage Index (VDI) total score and its seven individual items for lung damage (pulmonary hypertension; fibrosis; infarction; pleural fibrosis; chronic asthma; chronic breathlessness and impaired lung function), mortality and cause of death.

Statistical analysis

Chi-square test (or Fisher's exact test when appropriate) and Student's *t*-test were used to compare the qualitative and quantitative characteristics, respectively, among the seven studied primary vasculitides.

Ethics and approval committee

DCVAS was approved by institutional review boards at each participating institution. Written documentation of informed consent was obtained for each participant. Study procedures followed were in accordance with the 1983 revised Declaration of Helsinki. A specific research proposal for the use of DCVAS data for the present study was submitted and approved by the DCVAS Study Steering Committee.

Results

A total of 1952 patients with primary vasculitides were included in this analysis, including 170 patients with TAK, 657 with GCA, 555 with GPA, 223 with MPA, 146 with EGPA, 153 with IgAV and 48 with PAN. Their main disease and demographic characteristics are listed in Table 1.

Table 1 Characteristics of vasculitis in the study cohort

	TAK	GCA	GPA	MPA	EGPA	PAN	IgAV
Total number of patients	170	657	555	223	146	48	153
Gender, *n* (%)							
Male	28 (16.5)	225 (34.2)	287 (51.7)	98 (44.0)	78 (53.4)	27 (56.2)	85 (55.6)
Female	142 (83.5)	432 (65.8)	268 (48.3)	125 (56.0)	68 (46.6)	21 (43.8)	68 (44.4)
Age at diagnosis, mean (S.D.)	34.5 (12.1)	72.0 (9.1)	53.0 (16.5)	64.2 (13.2)	53.3 (15.2)	46.2 (19.1)	51.2 (21.0)
Ethnicity, no. of patients							
African	3	2	3	0	1	1	0
African American	0	3	1	2	2	0	0
Asian	13	7	20	49	10	2	14
Caucasian	10	56	76	29	32	9	13
European	38	554	314	104	72	21	107
Indian	40	2	38	5	9	3	3
Latin American	4	2	14	2	4	0	0
Middle Eastern	59	16	53	13	6	10	10
Other	8	20	48	22	13	2	6
History of smoking, *n* (%)	3 (1.8)	17 (2.6)	39 (7.0)	28 (12.6)	28 (19.2)	1 (2.1)	2 (1.3)
Comorbidities, *n* (%)							
Asthma	5 (2.9)	39 (5.9)	26 (4.7)	4 (1.8)	97 (66.4)	4 (8.3)	8 (5.2)
COPD	1 (0.6)	29 (4.4)	11 (2.0)	17 (7.6)	5 (3.4)	0	5 (3.3)
Serology, positive/available (%)							
cANCA	2/58 (3.4)	7/311 (2.3)	383/480 (79.8)	17/178 (9.6)	10/127 (7.9)	1/39 (2.6)	4/121 (3.3)
pANCA	1/60 (1.7)	20/301 (6.6)	55/456 (12.1)	163/183 (89.1)	58/129 (45.0)	3/41 (7.3)	7/123 (5.7)
PR3-ANCA	1/51 (1.9)	3/281 (1.1)	434/523 (83.0)	11/212 (5.2)	4/126 (3.2)	1/32 (3.1)	3/129 (2.3)
MPO-ANCA	0/52	9/284 (3.2)	47/503 (9.3)	201/216 (93.1)	65/129 (50.4)	0/32	3/132 (2.2)
anti-GBM	0/6	1/27 (3.7)	3/182 (1.6)	5/133 (3.8)	0/21	0/7	0/15
RF	6/55 (10.9)	22/264 (8.3)	135/313 (43.1)	56/144 (38.9)	40/93 (43.0)	6/28 (21.4)	4/107 (3.7)
ACPA	0/22	6/98 (6.1)	9/141 (6.4)	2/60 (3.3)	1/31 (3.2)	1/7 (14.3)	0/23
ANA	20/95 (21.1)	58/340 (17.1)	54/417 (12.9)	67/196 (34.2)	21/122 (17.2)	10/40 (25.0)	14/139 (10.1)

TAK: Takayasu's arteritis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic GPA; PAN: polyarteritis nodosa; IgAV, IgA vasculitis; COPD: chronic obstructive pulmonary disease; c: cytoplasmic; p: perinuclear; MPO: myeloperoxidase; anti-GBM: anti-glomerular basement membrane antibodies.

Table 2 Pulmonary manifestations in patients with different forms of vasculitis

	TAK	GCA	GPA	MPA	EGPA	PAN	IgAV
Clinical features, patients (%)							
Any respiratory symptom	37 (21.8)	104 (15.8)	358 (64.5)	147 (65.9)	130 (89.0)	13 (27.1)	9 (5.9)
Dyspnoea	25 (14.7)	51 (7.8)	232 (41.8)	97 (43.5)	96 (65.8)	9 (18.8)	4 (2.6)
Any cough	13 (7.6)	61 (9.3)	193 (34.8)	84 (37.7)	81 (55.5)	8 (16.7)	5 (3.3)
Dry cough	11 (6.5)	54 (8.2)	133 (24.0)	48 (21.5)	50 (34.2)	5 (10.4)	4 (2.6)
Productive cough	2 (1.2)	7 (1.1)	60 (10.8)	36 (16.1)	31 (21.2)	3 (6.3)	1 (0.7)
Haemoptysis	3 (1.8) [a]	2 (0.3)[a]	148 (26.7)	52 (23.3)	12 (8.2)	2 (4.2)	0
Pleuritic chest pain	3 (1.8)	6 (0.9)	43 (7.7)	13 (5.8)	7 (4.8)	2 (4.2)	0
Chest wall tenderness	1 (0.6)	1 (0.2)	10 (1.8)	1 (0.4)	3 (2.1)	0	0
Crackles on auscultation	2 (1.2)	10 (1.5)[b]	89 (16.0)	69 (30.9)	21 (14.4)	3 (6.3)	1 (0.7)
Wheezing on auscultation	2 (1.2)	7 (1.1)	24 (4.3)	13 (5.8)	79 (54.1)	0	2 (1.3)
Oxygen administered	2 (1.2)	1 (0.2)	44 (7.9)	32 (14.3)	14 (9.6)	3 (6.3)	1 (0.7)
Mechanical ventilation	0	0	15 (2.7)	6 (2.7)	5 (3.4)	0	0
Imaging findings, patients (%)							
Pulmonary imaging available	73 (42.9)	380 (57.8)	476 (85.8)	197 (88.3)	127 (87.0)	28 (58.3)	82 (53.6)
Normal imaging	64 (87.7)	309 (81.3)	197 (41.4)	54 (27.4)	38 (30.0)	18 (64.3)	73 (89.0)
Inflammation	2 (2.8)	12 (5.0)	65 (13.7)	46 (23.4)	39 (30.7)	0	1 (1.2)
Haemorrhage	0	0	30 (6.3)	19 (9.6)	1 (0.8)	1 (3.6)	0
Nodules	2 (2.8)	13 (3.4)	119 (25.0)[c]	23 (11.7)	17 (13.4)	0	1 (1.2)
Mass	0	1	47 (9.9)	0	0	0	0
Abscess	0	0	8 (1.7)	0	0	0	1 (1.2)
Consolidation	1 (1.4)	1	76 (16.0)	40 (20.3)	33 (26.0)	5 (17.9)	3 (3.7)
Fibrosis	0	6 (1.6)	9 (1.9)	49 (24.9)	8 (6.3)	0	1 (1.2)
Effusion	0	9 (2.3)	37 (7.8)	27 (13.7)	13 (10.2)	3 (10.7)	1 (1.2)

[a]In the 3 patients with TAK and 2 patients with GCA with haemoptysis, a previous history of COPD, smoking, congestive heart failure or productive cough was documented. [b]Ten patients with GCA had crackles on lung auscultation, with 7 of them being current or previous smokers, 2 having chronic obstructive pulmonary disease (COPD) and 3 having a positive test for pANCA. Out of these 10 patients, 7 had normal lung imaging, while 3 patients had fibrosis or atelectasis. [c]Clinical haemoptysis was reported by 36% of patients with GPA and pulmonary nodules. TAK: Takayasu's arteritis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic GPA; PAN: polyarteritis nodosa; IgAV: IgA vasculitis.

Respiratory symptoms

The frequencies of respiratory symptoms are presented in Table 2. Patients with AAV had more respiratory symptoms than patients with other vasculitides, with a frequency of 64.5, 65.9 and 89.0% for GPA, MPA and EGPA, respectively. Dyspnoea and cough were the most common respiratory symptoms. Wheezing was mostly reported in patients with EGPA.

Haemoptysis was reported in 26.7, 23.3 and 8.2% of patients with GPA, MPA and EGPA, respectively. The need for mechanical ventilation was only reported in patients with AAV, with a frequency of 2.7% for GPA, 2.7% for MPA and 3.4% for EGPA (all these patients were still alive at month 6).

Lung imaging

Lung imaging (Table 2) was mostly performed and/or reported in patients with AAV: GPA (85.8%), MPA (88.3%) and EGPA (87.0%). Only 42.9, 57.8, 58.3 and 53.6% of patients with TAK, GCA, PAN and IgAV had documented lung imaging, respectively.

Lung imaging was normal in most patients with IgAV (89.0%) and PAN (64.3%), but only in 41.4% of patients with GPA, 27.4% in those with MPA and 30.0% in those with EGPA. Nodules were reported in 25.0, 11.7 and 13.4% of patients with GPA, MPA and EGPA who underwent lung imaging studies, respectively. Lung masses and/or cavitating lesions were exclusively documented in patients with GPA (11.8%). Pulmonary fibrosis on imaging at diagnosis was documented in 1.9, 24.9 and 6.3% of patients with GPA, MPA and EGPA, respectively.

Imaging of pulmonary arteries was rarely documented in patients with LVV. Two patients with GCA had available pulmonary vascular imaging: one was normal and the other showed an aneurysm of the right pulmonary artery. Out of the 11 patients with TAK and available pulmonary artery imaging results, 4 were normal, 6 showed arterial wall thickening (4 bilateral, 2 on the left side only) and 1 had an increased FDG uptake of pulmonary arteries seen on PET.

Other respiratory investigations

As shown in Table 3, PFTs were mostly performed in patients with GPA (30.4%), MPA (20.6%) and EGPA (59.6%). A restrictive pattern was observed in 16.6, 28.3

TABLE 3 Results of pulmonary function tests, bronchoscopy and lung biopsy in patients with ANCA-associated vasculitis

	GPA	MPA	EGPA
Pulmonary function tests, patients (%)			
PFT available	169 (30.4)	46 (20.6)	87 (59.6)
Normal PFT	86 (50.9)	16 (34.8)	19 (21.8)
Restrictive pattern	28 (16.6)	13 (28.3)	4 (4.6)
Obstructive pattern	31 (18.3)	9 (19.6)	61 (70.1)
Low DLCO	27 (16.0)	21 (45.7)	8 (9.2)
Bronchoscopy findings, patients (%)			
Bronchoscopy available	144 (26.0)	34 (15.2)	31 (21.2)
Normal	36 (25.0)	9 (26.5)	9 (29.0)
Mass	6 (4.2)	0	0
Bronchial changes	59 (40.9)	6 (17.6)	13 (41.9)
Alveolar haemorrhage	61 (42.4)	22 (64.7)	3 (9.7)
Lung biopsy results, patients (%)			
Lung biopsy available	104 (18.9)	6 (2.7)	19 (13.0)
Normal	4 (3.8)	0	1 (5.3)
Non-diagnostic	12 (11.5)	2 (33.3)	7 (36.8)
Vasculitis	63 (60.6)	0	12 (63.2)
Inflammation	25 (24.0)	3 (50.0)	3 (15.8)
Fibrosis	3 (2.9)	1 (16.7)	0

GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic GPA; PFT: pulmonary function tests; DLCO: diffusion capacity for carbon monoxide.

and 4.6%, respectively, and an obstructive pattern in 18.3, 19.6 and 70.1%. A low DLCO was mostly observed in patients with MPA (45.7%), compared with 16.0% and 9.2% of patients with GPA or EGPA.

Bronchoscopy was performed in patients with GPA (26.0%), MPA (15.2%), EGPA (21.2%), PAN (6.4%) and IgAV (1.3%); none with GCA or TAK. In patients with AAV, 75% of the bronchoscopies were abnormal; blood was found in 42.4, 64.7 and 9.7% of patients with GPA, MPA and EGPA. Airway stenosis, including subglottic stenosis, tracheal and/or bronchial stenosis, was found in 16 (11.1%) patients with GPA who underwent bronchoscopy, but in none with MPA or EGPA.

Lung biopsies were performed in 104 (18.9%), 6 (2.7%) and 19 (13.0%) patients with GPA, MPA and EGPA. Vasculitis was found on biopsy in 63 (60.6%) patients with GPA, 12 (63.2%) patients with EGPA and in no patient with MPA. Non-specific inflammation was present in 25 (24.0%) of patients with GPA, 3 (50.0%) patients with MPA and 3 (15.8%) patients with EGPA. Fibrosis was found on biopsy in only 3 (2.9%) patients with GPA, 1 (16.6%) with MPA and none with EGPA. Biopsies were non-diagnostic in 12 (11.5%), 2 (33.3%) and 7 (36.8%) patients, respectively.

Vasculitis Damage Index

Lung damage at 6 months post-diagnosis was more frequent in patients with AAV; at least one pulmonary-VDI item was present in 15.4, 28.7 and 52.7% of patients with GPA, MPA and EGPA, respectively. The frequency of each pulmonary VDI item is detailed in Table 4. In patients with AAV with at least one item of lung damage, pulmonary fibrosis was present in 22.3, 62.5 and 2.6% of those with GPA, MPA or EGPA. In patients with EGPA, persistent chronic asthma was recorded at 6 months in 63 (43.2%) patients.

Pulmonary manifestations and autoantibodies

In patients with GPA, haemoptysis at baseline was more frequent in patients with positive PR3-ANCA as opposed to those with negative PR3-ANCA (21.4% *vs* 6.7%). The frequency of lung fibrosis in GPA did not vary according to ANCA positivity. Pulmonary nodules were more frequently observed in patients with GPA and positive ANCA, irrespective of the type ($P < 0.05$): 31.6% in patients with c-ANCA had nodules *vs* 18.5% in c-ANCA negative patients; 42.4% in p-ANCA positive *vs* 26.2% in p-ANCA negative patients; 30.6% in PR3-ANCA positive *vs* 19.3% in PR3-ANCA negative patients and 48.4% in MPO-ANCA positive *vs* 25.7% in MPO-ANCA negative patients.

In patients with MPA, the frequency of haemoptysis, pulmonary fibrosis and nodules did not vary significantly according to ANCA positivity.

In patients with EGPA, positive p-ANCA (58/129 patients) and MPO-ANCA (65/129 patients) were more frequently observed than positive c-ANCA (10/127 patients) and PR3-ANCA (4/126 patients). Pulmonary nodules in the presence of PR3-ANCA (75.0% *vs* 11.1% in PR3-ANCA negative patients). The frequency of pulmonary fibrosis did not vary significantly according to ANCA positivity.

Of the 924 patients with AAV, 336 were tested for anti-GBM and 8 (2.4%) were positive (dual positive for ANCA and anti-GBM). In these patients, pulmonary haemorrhage was observed in 37.5% (3/8 patients) *vs*

Table 4 Vasculitis Damage Index scores and individual items of pulmonary damage among patients with vasculitis

	TAK	GCA	GPA	MPA	EGPA	PAN	IgAV
VDI score, mean (S.D.)	1.9 (1.6)	0.77 (1.1)	1.9 (1.7)	2.1 (1.7)	2.4 (1.9)	1.5 (1.4)	0.5 (0.9)
VDI score in patients without pulmonary symptoms at baseline	1.8 (1.5)	0.8 (1.1)	1.8 (1.4)	1.5 (1.3)	1.1 (1.0)	1.3 (1.3)	0.5 (0.9)
VDI score in patients with pulmonary symptoms at baseline	2.49 (2.2)	0.7 (1.1)	1.9 (1.8)	2.4 (1.8)	2.6 (2.0)	2.1 (1.9)	1.1 (1.9)
Patients with ≥1 lung VDI item, *n* (%)	7 (4.1)	22 (3.3)	85 (15.4)	64 (28.7)	77 (52.7)	3 (6.2)	2 (1.3)
VDI items, no. of patients							
Pulmonary hypertension	4	0	2	2	1	0	0
Pulmonary fibrosis	0	1	19	40	2	0	0
Pulmonary infarction	3	0	0	1	0	1	0
Pleural fibrosis	0	0	3	0	0	0	0
Chronic asthma	1	3	4	2	63	0	0
Chronic dyspnoea	3	17	55	23	24	2	2
Abnormal pulmonary function tests	1	2	30	18	17	0	0

TAK: Takayasu's arteritis; GPA: granulomatosis with polyangiitis; MPA: microscopic polyangiitis; EGPA: eosinophilic GPA; PAN: polyarteritis nodosa; IgAV: IgA vasculitis; VDI: Vasculitis Damage Index.

7.3% in patients with AAV and negative anti-GBM ($P < 0.001$). Anti-GBM positivity did not influence the frequency of pulmonary VDI items at 6 months, including fibrosis, in patients with AAV.

Discussion

The DCVAS study was an international, collaborative effort to collect comprehensive clinical data on a large cohort of patients with various vasculitides, and offers detailed clinical, biological, radiological descriptions and short-term outcomes of patients with pulmonary manifestations. As expected, respiratory symptoms at baseline were more common in patients with AAV. Pulmonary involvement also led to more damage, mostly in AAV.

However, it is important to recognize that respiratory symptoms can also occur in patients with TAK, GCA, PAN or IgAV. In these patients, dyspnoea and cough were the two most common respiratory symptoms, as already reported in small series, and the pathophysiologic aetiologies of these findings are not always clear, especially in patients with LVV [22]. Therefore, clinicians should remain cautious as the differential diagnosis of respiratory symptoms is broad and may be unrelated to the underlying vasculitis. Vasculitis of the pulmonary artery has been reported more often in LVV, but was rarely observed in patients with TAK; however, only a few of them had documented imaging of these arteries.

The observed frequency of clinical haemoptysis in the DCVAS patients with AAV falls within the ranges previously described in smaller series (5–50%) [2–4, 8]. However, alveolar haemorrhage might be higher than reported since bronchoscopy was not performed in all patients with abnormal lung imaging, possibly missing subclinical alveolar haemorrhage. Haemoptysis was reported in all other forms of vasculitis, except in IgAV, despite existing cases in the literature [23]. However, one of the two patients with PAN and haemoptysis was p-ANCA positive (considered as having PAN by the investigator due to the presence of microaneurysms on vascular imaging) and the other had a normal bronchoscopy.

Pulmonary fibrosis was frequent in patients with MPA (24.6%), but much less in GPA (1.9%) or EGPA (6.3%). The longer-term incidence of lung fibrosis might be higher than reported here, as the follow-up duration was of only 6 months after the diagnosis of vasculitis. Lung imaging using CT-scan was not mandatory and plain chest radiograph may overlook or miss discrete, early changes of fibrosis. The occurrence of interstitial lung disease (with or without overt vasculitis) in patients with AAV, especially those with a positive MPO-ANCA, has been increasingly recognized and impacts survival [24–27]. In a series of 49 patients, the mortality rate in AAV with pulmonary fibrosis was as high as 37% after a median follow-up of 48 months, mainly due to respiratory insufficiency [6]. Similar data with other vasculitides is lacking.

At 6 months, only 43.2% of patients with EGPA had persistent chronic asthma recorded on the VDI. The short duration of follow-up, or the use of ongoing treatments, might explain this low rate. Discrepancies in how persistent asthma is interpreted (damage *vs* comorbidity), and recorded, between site investigators might also have contributed to this low reported percentage.

This study has several strengths. It is the largest, international study providing detailed information on pulmonary manifestations in systemic vasculitides. Data was collected in a standardized and systematic manner, providing valuable information on pulmonary symptoms, imaging, bronchoscopy, PFTs, biopsy and 6-month outcomes. Additionally, the DCVAS cohort provides 'real-world' data that is highly generalizable given the broad involvement of 136 centres in 32 countries and

investigators from multiple specialties. Our study shows that pulmonary manifestations vary according to the type of vasculitis and may be useful to differentiate between different AAV [28].

There are several limitations to consider. This analysis included patients for whom the investigator was 'very certain' of the diagnosis, possibly reducing the generalizability of its findings. The DCVAS study had a short duration of follow-up, which may lead us to underestimate the cumulative pulmonary damage caused by the vasculitis. Investigations including imaging, PFTs, bronchoscopy and lung biopsy were not standardized in all patients; the frequency of findings must therefore be interpreted with caution as patients were more likely to be investigated if the clinician had a suspicion of pulmonary disease. Symptoms and investigation findings entered in the database had to be attributable to the vasculitis; however, there is a chance that some findings documented were unrelated and caused by another disease. Finally, data was entered either prospectively, at diagnosis, or retrospectively within the first 2–5 years after diagnosis of their vasculitis, which might be prone to recall bias or depend on the completeness of previous recordkeeping and prevented more analyses of short-term outcomes. Mortality was, for example, not analysed in detail in this study, because many patients were enrolled after month 6 post-diagnosis (possible 'survivor bias') [29].

Conclusion

Pulmonary manifestations occur in many primary systemic vasculitides, but at variable frequencies and with various presentations. In patients with AAV, pulmonary manifestations are frequent, often severe and the source of permanent damage. In patients with TAK, GCA, IgAV or PAN, pulmonary manifestations can occur but less commonly lead to lung damage. Clinicians caring for patients with vasculitis need to be aware of the full spectrum of potential pulmonary manifestations of these complex diseases.

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Henes, University of Tuebingen, Germany; Joanna Hepburn, NHS Greater Glasgow & Clyde, UK; Vera Herd, NHS Grampian, UK; Christoph Hess, Universität Basel, Switzerland; Catherine Hill, Queen Elizabeth Hospital, Australia; Andrea Hinojosa-Azaola, Instituto Nacional de Ciencias Médicas y Nutrición Salvador Zubirán, Mexico; Junichi Hirahashi, University of Tokyo Hospital, Japan; Fumio Hirano, Tokyo Medical and Dental University Hospital, Japan; Alojzija Hocevar, University Medical Centre Ljubljana, Slovenia; Julia Holle, Klinikum Bad Bramstedt, Germany; Nicole Hollinger, Kreiskliniken Esslingen, Germany; Sakae Homma, Toho University Hospital, Japan; Theresa Howard, University of Kansas Medical Center Research Institute, USA; Rachel K. Hoyles, Oxford University Hospitals NHS Foundation Trust, UK; Zdenka Hruskova, General University Hospital, Prague, Czech Republic; Gayle Hutcheon, NHS Grampian, UK; Maria Ignacak, University of Jagiellonian, Poland; Annette Igney-Oertel, University of Tuebingen, Germany; Kei Ikeda, Chiba University, Japan; Noriko Ikegaya, Kyorin University Hospital, Japan; Samyukta Jagadeesh, Mount Sinai Hospital, Toronto, Canada; Jane Jaquith, Mayo Clinic, USA; David R. W. 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Luqmani, Oxford University Hospitals NHS Foundation Trust, UK; Amanda Lyle, Mid Essex Hospital Services NHS Trust, UK; Matthew MacDonald, University of Pennsylvania, USA; Sarah L. Mackie, Leeds Teaching Hospitals & University of Leeds, UK; Leah Madden, University of Pennsylvania, USA; Malgorzata Magliano, Buckinghamshire Heathcare NHS Trust, Stoke Mandeville Hospital, UK; Hirofumi Makino, Okayama University Hospital, Japan; Ashima Makol, Mayo Clinic, USA; Ritu Malaiya, Epsom and St Helier University Hospitals NHS Trust, UK; Anshuman Malaviya, Mid Essex Hospital Services NHS Trust, UK; Ramesh Manthri, Nizam's Institute of Medical Sciences, India; Federica Maritati, University of Parma, Italy; Ana Martins da Silva, Centro Hospitalar do Porto, Portugal; Justin C. Mason, Imperial College Healthcare NHS Trust, UK; Cecilia Matara, Cambridge University Hospitals NHS Foundation Trust, UK; Kazuo Matsui, Kameda Medical Centre, Japan; Eric L. Matteson, Mayo Clinic, USA; Dawn McBride, University of Pittsburgh, USA; Keith McCullough, York Teaching Hospitals NHS Foundation Trust, UK; Lucy McGeoch, NHS Greater Glasgow & Clyde, UK; John McLaren, NHS Fife, UK; Caitlin McMillian, University of Kansas Medical Center Research Institute, USA; Naval Mendiratta, Medanta Delhi, India; Ajit Menon, Staffordshire & Stoke on Trent Partnership NHS Trust, UK; Dimos Merinopoulos, Southend University Hospital NHS Foundation Trust, UK; Peter A. Merkel, Boston University, USA; Peter Merkel, University of Pennsylvania, USA; Sandra Messier, St. Joseph's Healthcare Hamilton, Canada; Robert G. Micheletti, University of Pennsylvania, USA; Karen Mills, Norfolk and Norwich University Hospitals NHS Foundation Trust, UK; Nataliya Milman, University of Ottawa, Canada; Masahiro Minoda, Kameda Medical Centre, Japan; Ranjana Walker Minz, PGIMER, Chandigarh, India; Claudia Möck, Klinikum Bad Bramstedt, Germany; Aladdin J. 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Urban, University of Parma, Azienda Ospedaliero, Italy; Joichi Usui, Tsukuba University Hospital, Japan; Augusto Vaglio, University of Parma, Azienda Ospedaliero, Italy; Srinivasan Venkatachalam, Royal Wolverhampton NHS Trust, UK; Erin Vermaak, Staffordshire & Stoke on Trent Partnership NHS Trust, UK; Vishad Viswanath, Christian Medical College & Hospital, India; Takashi Wada, Kanazawa University Hospital, Japan; Shrikant Wagh, Jehangir Clinical Development Centre, India; Daniel J. Wallace, Cedars-Sinai Medical Center, USA; Giles Walters, Canberra Hospital, Australia; Bastian Walz, Kreiskliniken Esslingen, Germany; Jin Wan, Anzhen Hospital, Capital Medical University, China; Tian Wang, Anzhen Hospital, Capital Medical University, China; Guochun Wang, China–Japan Friendship Hospital, China; Kenneth J. Warrington, Mayo Clinic, USA; Richard A. Watts, East Suffolk & North Essex NHS Foundation Trust, UK; Katarzyna Wawrzycka-Adamczyk, University of Jagiellonian, Poland; Praveen Weeratunga, University of Colombo Medical Unit, Sri Lanka; Michael H. Weisman, Cedars-Sinai Medical Center, USA; Sugeesha Wickramasinghe, University of Colombo Medical Unit, Sri Lanka; Mark Williams, Southend University Hospital NHS Foundation Trust, UK; Megan Williams, Auckland District Health Board, New Zealand; Krzysztof Wojcik, University of Jagiellonian, Poland; Laticia Woodruff, University of Alabama, Birmingham,

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Data availability statement

Data from the DCVAS study used for analysis of this study are available from the corresponding author after consultation with the DCVAS steering committee on reasonable request. The data are not publicly available because of ethical restrictions.

References

1 Frankel SK, Cosgrove GP, Fischer A, Meehan RT, Brown KK. Update in the diagnosis and management of pulmonary vasculitis. Chest 2006;129:452–65.

2 Manganelli P, Fietta P, Carotti M, Pesci A, Salaffi F. Respiratory system involvement in systemic vasculitides. Clin Exp Rheumatol 2006;24:S48–59.

3 Adams TN, Zhang D, Batra K, Fitzgerald J. Pulmonary manifestations of large, medium, and variable vessel vasculitis. Respir Med 2018;145:182–91.

4 Lally L, Spiera RF. Pulmonary vasculitis. Rheum Dis Clin North Am 2015;41:315–31.

5 Langford CA, Sneller MC, Hallahan CW *et al.* Clinical features and therapeutic management of subglottic stenosis in patients with Wegener's granulomatosis. Arthritis Rheum 1996;39:1754–60.

6 Comarmond C, Crestani B, Tazi A *et al.* Pulmonary fibrosis in antineutrophil cytoplasmic antibodies (ANCA)-associated vasculitis: a series of 49 patients and review of the literature. Medicine (Baltimore) 2014;93:340–9.

7 Cottin V, Bel E, Bottero P et al.; the Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERM"O"P). Respiratory manifestations of eosinophilic granulomatosis with polyangiitis (Churg-Strauss). Eur Respir J 2016;48:1429–41.

8 Hassan TM, Hassan AS, Igoe A *et al.* Lung involvement at presentation predicts disease activity and permanent organ damage at 6, 12 and 24 months follow-up in ANCA-associated vasculitis. BMC Immunol 2014;15:20.

9 Yang L, Zhang H, Jiang X *et al.* Clinical manifestations and longterm outcome for patients with Takayasu arteritis in China. J Rheumatol 2014; 41:2439–46.

10 Kong X, Ma L, Lv P *et al.* Involvement of the pulmonary arteries in patients with Takayasu arteritis: a prospective study from a single centre in China. Arthritis Res Ther 2020;22:131.

11 Baldwin C, Mohammad A, Cousins C *et al.* Long-term outcomes of patients with Takayasu arteritis and renal artery involvement: a cohort study. Rheumatol Adv Pract 2018;2:1–7.

12 Larson TS, Hall S, Hepper NG, Hunder GG. Respiratory tract symptoms as a clue to giant cell arteritis. Ann Intern Med 1984;101:594–7.

13 Zenone T, Souquet PJ, Bohas C, Durand DV, Bernard JP. Unusual manifestations of giant cell arteritis: pulmonary nodules, cough, conjunctivitis and otitis with deafness. Eur Respir J 1994;7:2252–4.

14 Nick J, Tuder R, May R, Fisher J. Polyarteritis nodosa with pulmonary vasculitis. Am J Respir Crit Care Med 1996;153:450–3.

15 Matsumoto T, Homma S, Okada M *et al.* The lung in polyarteritis nodosa: a pathologic study of 10 cases. Hum Pathol 1993;24:717–24.

16 Guo X, Gopalan R, Ugbarugba S *et al.* Hepatitis B-related polyarteritis nodosa complicated by pulmonary hemorrhage. Chest 2001;119:1608–10.

17 Menon Y, Singh R, Cuchacovich R, Espinoza LR. Pulmonary involvement in hepatitis B-related polyarteritis nodosa. Chest 2002;122:1497–8.

18 Nadrous HF, Yu AC, Specks U, Ryu JH. Pulmonary involvement in Henoch-Schönlein purpura. Mayo Clin Proc 2004;79:1151–7.

19 Cream J, Gumpel JM, Peachey RD. Schönlein-Henoch purpura in the adult: a study of 77 adults with anaphylactoid or Schönlein-Henoch purpura. Q J Med 1970;39:461–84.

20 Rajagopala S, Shobha V, Devaraj U, D'Souza G, Garg I. Pulmonary hemorrhage in Henoch-Schönlein purpura: case report and systematic review of the English literature. Semin Arthritis Rheum 2013;42:391–400.

21 Craven A, Robson J, Ponte C *et al.* ACR/EULAR-endorsed study to develop Diagnostic and Classification Criteria for Vasculitis (DCVAS). Clin Exp Nephrol 2013;17:619–21.

22 Kondo T, Ohira Y, Uehara T *et al.* Cough and giant cell arteritis. QJM 2018;111:747–8.

23 Ito Y, Arita M, Kumagai S *et al.* Diffuse alveolar hemorrhage in IgA vasculitis with an atypical presentation. Intern Med 2018;57:81–4.

24 Arulkumaran N, Periselneris N, Gaskin G *et al.* Interstitial lung disease and ANCA-associated vasculitis: a retrospective observational cohort study. Rheumatology 2011;50: 2035–43.

25 Katsumata Y, Kawaguchi Y, Yamanaka H. Interstitial lung disease with ANCA-associated vasculitis. Clin Med Insights Circ Respir Pulm Med 2015;9:51–6.

26 Kishore N, Gupta N, Dhar A, Abrari A, Rath P. Interstitial lung disease with usual interstitial pneumonia pattern preceding the presentation of ANCA-associated vasculitis by 4 years: coincidence or correlation? Breathe 2018;14:e105–e110.

27 Huang H, Wang YX, Jiang CG *et al.* A retrospective study of microscopic polyangiitis patients presenting with pulmonary fibrosis in China. BMC Pulmonary Med 2014;14:(81–6.

28 Robson J, Grayson P, Ponte C *et al.* OP0021 Draft classification criteria for the ANCA associated vasculitides. Ann Rheum Dis 2018;77:60–1.

29 Demiselle J, Auchabie J, Beloncle F *et al.* Patients with ANCA-associated vasculitis admitted to the intensive care unit with acute vasculitis manifestations: a retrospective and comparative multicentric study. Ann Intensive Care 2017;7:39.