Impact of concurrent glomerulonephritis on outcomes of diffuse alveolar haemorrhage in antineutrophil cytoplasmic antibody-associated vasculitis

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Abstract

Objective

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) commonly presents with diffuse alveolar haemorrhage (DAH) and/or glomerulonephritis. Patients who present with DAH but without kidney involvement have been understudied.

Methods

Patients with DAH diagnosed by bronchoscopy and attributed to AAV over 8.5 years were retrospectively identified through electronic medical records and bronchoscopy reporting software. Patients with end-stage kidney disease (ESKD) or prior kidney transplant were excluded. Characteristics, treatments, and outcomes were abstracted.

Results

30 patients were identified with DAH secondary to AAV. Five with ESKD or prior kidney transplant, and one with concomitant anti-glomerular basement membrane disease, were excluded, leaving 24 patients for analysis. At the time of qualifying bronchoscopy, six patients had no apparent kidney involvement by AAV, while eight of 18 with kidney involvement required dialysis. Of the eight patients dialysed during the initial hospitalisation, four were declared to have ESKD and three died in the subsequent year (one of whom did both). None of the 16 patients without initial dialysis requirement developed kidney involvement requiring dialysis in the subsequent year, though three of the six without initial evidence of kidney involvement by AAV ultimately developed it. No patient without initial kidney involvement died during follow-up.

Conclusion

In our cohort, patients with DAH due to AAV without initial kidney involvement did not develop kidney involvement requiring dialysis or die during the follow-up period, though half of patients without initial evidence of kidney involvement subsequently developed it. Larger studies are warranted to better characterise this population and guide medical management.

Key words

ANCA-associated vasculitis, glomerulonephritis, end-stage kidney disease, haemoptysis

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Introduction

Antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) commonly presents with diffuse alveolar haemorrhage (DAH) and/or glomerulonephritis (1). While DAH can carry high short-term mortality, longer-term survival in AAV is tied primarily to kidney involvement and treatment complications such as infection (2-6). Death and development of end-stage kidney disease (ESKD) at one year are outcomes typically used in AAV clinical trials to assess efficacy of treatment (7-9). Optimal management of patients with DAH due to AAV remains unclear, and data are particularly lacking for patients who present with DAH without concurrent kidney involvement, an important subset representing up to half of patients with DAH due to AAV (10-14). Using bronchoscopy findings for a well-defined cohort, we aim to compare the characteristics and outcomes of patients with DAH due to AAV with and without concurrent kidney involvement.

Materials and methods

Patients who underwent flexible bronchoscopy at our institution from January 1, 2012, through November 30, 2020, were identified by search of bronchoscopy documentation (Provation; Minneapolis, MN, USA) with the terms "blood(y)," "bleeding," or "progressively," clinical notes including "alveolar haemorrhage" or "DAH," and/or ICD-9 or ICD-10 billing codes for haemoptysis or pulmonary haemorrhage (786.30, R04.2, or R04.89). Patients were excluded if there was no bronchoalveolar lavage (BAL) performed, the BAL return was not bloody or not described (and without cytologic description of hemosiderin-laden macrophages), the blood was thought by the proceduralist to be of non-alveolar origin, or the patient was a lung transplant recipient. Electronic medical records (EMR) for included patients were then manually reviewed for evidence of AAV consistent with Chapel Hill consensus classification criteria, and full data collection was completed for these patients (1). Final adjudication regarding attribution of DAH to AAV was determined by at least two investigators after thorough EMR review. Patients with ESKD or prior kidney transplant were excluded.

The Birmingham Vasculitis Activity Score version 3 (BVASv3) and Simplified Acute Physiology Score II (SAPS II) were calculated as measures of disease severity (15-16). Estimated glomerular filtration rate was calculated using the Cockroft-Gault equation (17). Patients were considered to have clinically relevant kidney involvement by AAV if they had any BVASv3 renal subsection item felt by the treating team to be due to active AAV. The primary outcomes of interest were death, kidney involvement, or the need for dialysis within one year of the qualifying bronchoscopy. Respiratory morbidity was assessed with need for intensive care unit (ICU) admission, ICU length of stay, need for mechanical ventilation, and ventilator-free days in the first 30 days after the qualifying bronchoscopy. Descriptive statistics were used for baseline demographic and clinical variables. For each variable, patients with missing data were excluded. Analyses were performed using the SAS software package, v. 9.4 (SAS Institute Inc.; Cary, NC, USA).

This study was approved by the Institutional Review Board at The Ohio State University (2018H0319).

Results

Patient identification is presented in Figure 1. Bronchoscopy documentation yielded 1034 patients, with an additional 941 identified by EMR clinical notes search, resulting in 1975 unique patients with evidence of blood in BAL. Among these 1975 patients, 394 had BALs characterised as persistently or progressively bloody, 1381 as blood-tinged, and 200 were described as having a non-alveolar source of bleeding. Among those with blood-tinged BAL return, 68 were suspected of having DAH by the clinical team. These 68, along with those having persistently or progressively bloody return, were reviewed, resulting in 30 patients who were identified as having DAH secondary to AAV. One patient with anti-glomerular basement membrane (GBM) disease overlap was excluded, as were five patients with

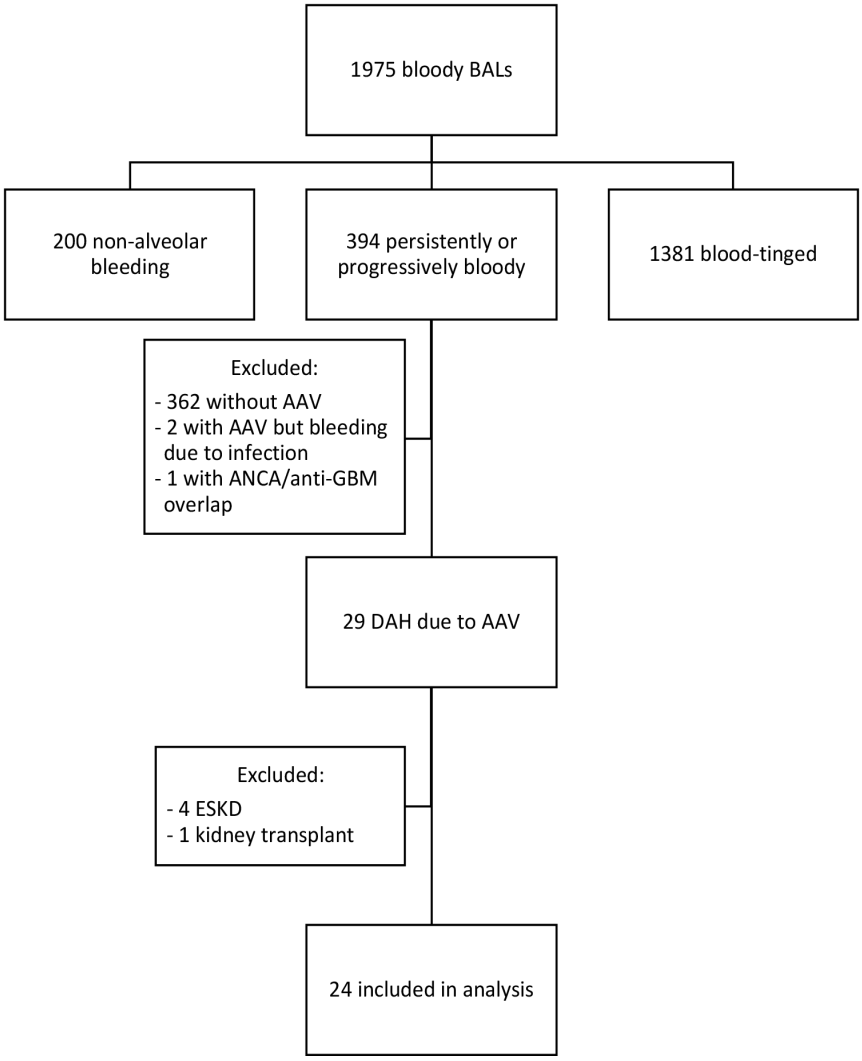

Fig. 1. Patient identification.
BAL: bronchoalveolar lavage; AAV: antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis; GBM: glomerular basement membrane; DAH: diffuse alveolar haemorrhage; ESKD: end-stage kidney disease.

ESKD (one of whom had undergone kidney transplant), resulting in 24 patients for the final analysis.

Characteristics of the 24 included patients with DAH due to AAV with and without kidney involvement are outlined in Table I. Eighteen patients (75%) had apparent kidney involvement of AAV at the time of the BAL identifying DAH, including ten with glomerulonephritis confirmed on biopsy. Age, sex, and race were similar between patients with versus without kidney AAV. A total of seven patients (29%) across both groups had a prior history of AAV, and two additional patients had a prior diagnosis of other autoimmune disease. Eight of the nine patients with pre-existing AAV or autoimmune diagnoses were on prednisone and/or an additional immunosuppressant at presentation. All 24 included patients were ANCA-positive by immunofluorescence and/or antigen-specific testing. Haemoglobin was lower in patients with kidney involvement by AAV. The distribution of additional organ involvement by AAV was similar between the two groups, including general/constitutional (54% of total), ear/nose/throat (25%), cutaneous (17%), and mucous membrane/eye (12%) manifestations.

Most (67%) patients were admitted to the ICU, occurring more frequently in patients with kidney AAV (78%) than without kidney AAV (33%). A minority of patients in each group required mechanical ventilation; patients without kidney AAV had more ventilator-free days.

Outcomes within one year of the identification of DAH are presented in Table I and Figure 2. Eight of the 18 patients with kidney involvement required haemodialysis acutely and four were ultimately declared to have ESKD within the year. Across both groups, none of the 16 patients without initial dialysis requirement developed kidney involvement requiring dialysis in the subsequent year. Two of the six patients without apparent kidney involvement at the time of DAH identification went on to develop clinically apparent kidney involvement within two weeks of the bronchoscopy despite initiation of systemic immunosuppression; neither required dialysis. No clear clinical characteristics or data distinguished these two patients from the remainder of patients without initial kidney AAV. No other patients without initial kidney involvement developed it within the subsequent year, though an additional patient developed kidney involvement approximately two years after the bronchoscopy identifying DAH.

While recurrent DAH was diagnosed in one patient in each group, serious infections occurred in a higher proportion of patients with initial kidney involvement by AAV, though this difference did not meet statistical significance.

One patient with acute dialysis requirement died during the index hospitalisation and three other patients died within the subsequent year - two who had required acute dialysis and one with initial kidney involvement not requiring dialysis. No patients without kidney involvement by AAV at the time of their qualifying DAH died in the next year.

Discussion

This single-centre retrospective cohort study highlights important differences between patients with DAH due to AAV with and without concurrent kidney involvement, the latter of which has not been a focus of prior research. Patients without kidney involvement had lower overall disease severity, were less likely to require ICU admission, had more ventilator-free days, and had better out-

Table I. Patient characteristics.

	Full cohort (n=24)	Kidney AAV (n=18)	No kidney AAV (n=6)	*p*-value
Baseline characteristics				
Age in years, median (IQR)	58 (53, 70)	56 (53, 70)	64 (58, 65)	0.401
Female sex, n (%)	13 (54%)	8 (44%)	5 (83%)	0.098
White race, n (%)	23 (96%)	18 (100%)	5 (83%)	0.077
History of smoking, n (%)	13 (54%)	10 (56%)	3 (50%)	0.813
Relapsing vasculitis, n (%)	7 (29%)	5 (28%)	2 (33%)	0.795
Chronic kidney disease, n (%)	6 (25%)	5 (28%)	1 (17%)	0.586
Lab results				
Haemoglobin (g/dL), median (IQR)	8.2 (7.5, 9.7)	8.2 (7.5, 9.1)	9.7 (7.8, 11.4)	**0.028**
ANCA				0.152
c-ANCA and/or anti-PR3	14 (58%)	12 (67%)	2 (33%)	
p-ANCA and/or anti-MPO	10 (42%)	6 (33%)	4 (67%)	
Kidney manifestations				
Creatinine (mg/dL), median (IQR)	2.8 (0.9, 6.2)	3.0 (1.0, 6.3)	1.0 (0.9, 1.1)	0.057
eGFR (mL/min), median (IQR)	54 (16, 92)	25 (14, 80)	76 (54, 171)	0.303
Presence of haematuria, n (%)	15 (63%)	15 (83%)	0 (0%)	**<0.001**
Presence of proteinuria, n (%)	11 (46%)	11 (61%)	0 (0%)	**0.009**
Kidney biopsy results, n (%)				**0.022**
Glomerulonephritis	10 (42%)	10 (56%)	0 (0%)	
Other kidney disease	1 (4%)	0 (0%)	1 (17%)	
No biopsy performed	13 (54%)	8 (44%)	5 (83%)	
Required acute dialysis, n (%)	8 (33%)	8 (44%)	0 (0%)	**0.046**
Severity of illness				
BVASv3, median (IQR)	24 (18, 32)	26 (24, 34)	15 (11, 17)	**<0.001**
SAPS II, median (IQR)	24 (18, 33)	30 (20, 47)	20 (13, 22)	0.057
Hospital admission, n (%)	22 (92%)	17 (94%)	5 (83%)	0.394
ICU admission, n (%)	16 (67%)	14 (78%)	2 (33%)	**0.046**
ICU length of stay, median (IQR)	8 (6, 12)	8 (7, 11)	7 (2, 12)	0.599
Required supplemental oxygen, n (%)	18 (75%)	15 (83%)	3 (50%)	0.476
Required mechanical ventilation, n (%)	9 (38%)	8 (44%)	1 (17%)	0.224
Ventilator-free days, median (IQR)	30 (24, 30)	30 (23, 30)	30 (29, 30)	**0.024**
Initial treatment				
Enteral steroids, n (%)	24 (100%)	18 (100%)	6 (100%)	-
Intravenous steroids, n (%)	19 (79%)	15 (83%)	4 (67%)	0.384
Enteral cyclophosphamide, n (%)	13 (54%)	12 (67%)	1 (17%)	**0.033**
Intravenous cyclophosphamide, n (%)	3 (13%)	3 (17%)	0 (0%)	0.285
Rituximab, n (%)	7 (29%)	4 (22%)	3 (50%)	0.195
Intravenous immunoglobulin, n (%)	6 (25%)	5 (28%)	1 (17%)	0.586
Plasma exchange, n (%)	11 (46%)	10 (56%)	1 (17%)	0.098
One-year outcomes				
Required outpatient dialysis, n (%)	6 (26%)*	6 (33%)	0 (0%)	0.262
Declared ESKD, n (%)	4 (17%)	4 (22%)‡	0 (0%)	0.264
Deceased, n (%)	4 (17%)	4 (22%)	0 (0%)	0.206
Recurrent DAH, n (%)	2 (8%)	1 (6%)	1 (17%)	0.431
Serious infection, n (%)	8 (33%)	7 (39%)	1 (17%)	0.232

*n=23 patients. One patient died prior to discharge.
‡Three patients died before they could be declared ESKD.
ANCA: antineutrophil cytoplasmic antibody; AAV: ANCA-associated vasculitis; IQR: interquartile range; c-ANCA: cytoplasmic ANCA staining pattern; PR3: proteinase 3; p-ANCA: perinuclear ANCA staining pattern; MPO: myeloperoxidase; eGFR: estimated glomerular filtration rate; BVASv3: Birmingham Vasculitis Activity Score version 3; SAPS: Simplified Acute Physiology Score; ICU: intensive care unit; ESKD: end-stage kidney disease; DAH: diffuse alveolar haemorrhage.

comes overall. This is an important distinction because although DAH can be life-threatening, infections are the leading cause of death in AAV, particularly in the first year, highlighting the crucial need to balance the risks and benefits of immunosuppression (3-6). Importantly, recurrent DAH did occur and two patients developed apparent kidney involvement shortly after identification of DAH despite initiation of immunosuppression. Further work to identify predictors of specific organ involvement, additional non-kidney outcome measures, and treatment approaches incorporating these are warranted.

Our study has multiple limitations, in addition to its retrospective nature. While the number of patients with DAH due to AAV per year is similar to other published reports, AAV is an uncommon disease and the small total number of patients limits the robustness of our conclusions and our ability to evaluate treatment effects (12-14). Our requirement of bronchoscopy for inclusion, while strengthening the diagnoses, also likely limited the total number of patients. Not all patients had kidney biopsies, so it is possible that some were misclassified. Finally, there was minimal racial or ethnic diversity in our cohort, potentially limiting the generalisability of our findings.

In conclusion, patients with DAH due to AAV without initial kidney involvement did not develop kidney involvement requiring dialysis or die in the subsequent year, and no patients newly developed dialysis requirement within one year of their presentation with DAH. Larger studies are needed to better characterise the risks of death and ESKD in patients with DAH, as well as additional patient-important outcomes, in order to guide individualised management decisions in AAV.

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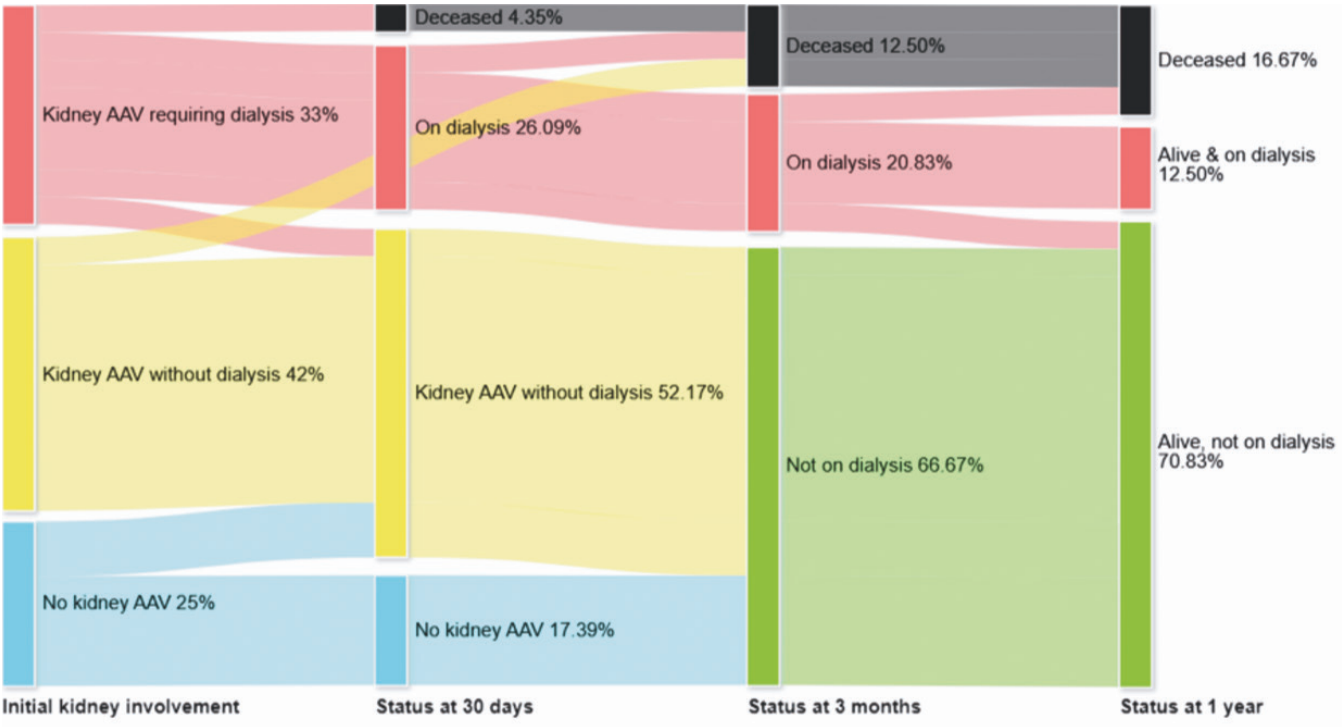

Fig. 2. Outcomes stratified by kidney involvement.

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