Alveolar haemorrhage in ANCA-associated vasculitides: 80 patients' features and prognostic factors

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ABSTRACT

Objective. *Alveolar haemorrhage (AH) can be a mild or life-threatening manifestation of antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV), but its prognostic impact and specific characteristics remain controversial. Our objective was to determine the prognostic value of AH in this context.*

Methods. *AH episodes that occurred, between 1991 and 2010, in AAV patients entered in the FVSG database were retrospectively analysed. Data on AH characteristics and outcome measures were collected on a specific form.*

Results. *Among the 80 cases analysed, AAV were 61.25% granulomatosis with polyangiitis (GPA) (Wegener), 26.25% microscopic polyangiitis (MPA), 10% Churg-Strauss syndrome and 2 (2.5%) unclassified. Mild or severe haemoptysis alone, or together with other clinical symptoms was present in 77 (96.2%) patients before AAV diagnosis. Among 10 (12.5%) patients requiring mechanical ventilation, 4 had prior minor haemoptysis before abundant AH. Sixty-one (76.3%) patients had concomitant active rapid crescentic glomerulonephritis causing renal insufficiency (pulmo-renal syndrome): 37/49 GPA (Wegener) (75.5% of all GPA (Wegener)), 19/21 MPA (90.4% of all MPA), 3/8 had CSS and 2/2 had unclassified vasculitis. The mean AH-to-treatment-onset interval was 5.9 days. Mean follow-up was 7.3 years. Forty-seven (58.8%) patients relapsed: 23 with AH and with (13) or without (10) other organ involvement, 24 with non-AH manifestation(s). Three patients underwent kidney transplantation. Sixteen (20%, 8 GPA (Wegener) and 8 MPA) patients died. No death resulted directly from the initial AH; 14 (87.5%) patients with pulmo-renal syndrome died.*

Conclusion. *As previously demonstrated by the Five-Factor Score, AH alone is not predictive of poor prognosis, unlike kidney involvement, which dictates a poor outcome.*

Introduction

Granulomatosis with polyangiitis (Wegener) (GPA (Wegener)), microscopic polyangiitis (MPA) and Churg-Strauss syndrome (CSS), antineutrophil cytoplasm antibody (ANCA)-associated vasculitides (AAV), are a group of systemic autoimmune diseases histologically characterised by inflammation of small-vessel walls (1). The lungs and kidneys can be severely affected. When alveolar capillary basement-membrane integrity is breached as a consequence of immune-mediated inflammation and destruction, red blood cells enter the alveolar spaces, resulting in diffuse alveolar haemorrhage (AH) (2). Concomitant AH and acute glomerulonephritis is known as the pulmo-renal syndrome (3), one of the most severe AAV manifestations (4, 5). AH can be mild or life-threatening. Although no factors predicting the development of one or the other clinical form have been identified, it can be considered that older age, comorbidities and the extent of alveolar bleeding negatively influence the clinical outcome. In an attempt to stratify AAV prognoses, we previously established the Five-Factor Score (FFS) (6), which is able to predict survival and outcome based on different vasculitis manifestations (renal insufficiency, cardiomyopathy, gastrointestinal and age >65 years and the absence of ear, nose and throat symptoms). The objective of this study was not to give epidemiological information on AH occurring in AAV but to better characterise specific manifestations and prognostic features based on

this retrospective analysis of 80 vasculitis patients who experienced AH.

Patients and methods

Patients

AH episodes occurring between 1981 and 2010 in AAV patients entered in the FVSG database, and for whom complete information and follow-up were obtained, were analysed retrospectively. Included patients had histologically proven small-vessel necrotising vasculitides or fulfilled the American College of Rheumatology criteria and/or the Chapel Hill Consensus nomenclature (1, 7, 8). The cardinal event leading to AH diagnosis was: minor or major haemoptysis (for the vast majority of patients) and/or respiratory insufficiency together with, at least, one compatible complementary diagnostic tests (x-ray, computed-tomography (CT) scan, and/or bronchoscopy and/or bronchoalveolar lavage (BAL)). Bronchoscopy was performed to differentiate, especially for minor haemoptysis, an upper respiratory tract cause of bleeding from AH.

Methods

We sent a detailed questionnaire to treating physicians and FSVG members who had included the patients. If, for any reason, they were unwilling or unable to complete the form themselves, we requested that they send us a copy of the patient's chart so that we could collect the information ourselves. The FVSG database was established in 1981 and contains data on patients included in prospective therapeutic trials organised since 1981, patients treated out of prospective trials and patients followed in other hospitals by clinician FVSG members who filled out the initial files and regularly updated the FVSG databank. The latter group comprised patients included on a voluntary basis by members of the FVSG.

For all patients, name, sex, date of birth, systemic vasculitis diagnosed, date of diagnosis, initial symptoms and date they appeared were available in the FSVG database. The questionnaire was a straightforward 5-page booklet seeking the following information: comorbidities at the time of AH (smoking history, heart failure, lung cancer, pulmonary embolism). Features of the first minor bloody sputum episodes, often neglected, preceding symptoms defining AH and satisfying the following characteristics were carefully examined: haemoptysis; AH-compatible chest x-ray and CT scan (presence of ground-glass images) results; AH-caused hypoxia; serum haemoglobin decline ≥1 g/dl during the first 48 hours after AH; mechanical ventilation required; bronchoscopy and BAL, if performed, results (bloody discoloration, total number of cells recovered, percentage >20% of haemosiderin-laden macrophages and siderophages, and Golde score >20). Other symptoms were also noted, *e.g.* epistaxis and/or haematemesis preceding the AH episode, renal insufficiency at the time of AH (serum creatinine >140 μmol/L, as a surrogate of glomerulonephritis). A pulmonary biopsy showing capillaritis (at any time during AAV) confirmed the AAV diagnosis, when needed. In the context of AH, when renal symptoms were present, a renal biopsy showing pauci-immune glomerulonephritis was taken to mean that concomitant AH was a vasculitis manifestation.

We also collected information on treatments prescribed during AAV: AH diagnosis, acute and maintenance phase and AAV relapses, if any. ANCA were sought by immunofluorescence, then enzyme-linked immunosorbent assays (ELISA) were run to determine their anti-proteinase-3 or anti-myeloperoxidase antibody specificity for each patient. For the patients who had been included in the database when ANCA were not systematically tested or when ANCA specificity was not systematically determined, we tested samples from our serum bank, when available. Despite retrospective serum analyses, some ANCA results are missing. Anti-glomerular basement-membrane antibodies were also sought for all patients. Data were collected by one of us (AK) and checked by a second investigator (LG).

Treatment was not codified and followed the usual recommendations for AAV therapy. Only part of the patients had participated in prospective trials organised by the FVSG. Patients were treated in hospitals (university or general) and not specifically in referral centres, sometimes in intensive care units, depending on the severity of their clinical manifestations.

Results

Demographics

Eighty patients with AH secondary to AAV, predominantly males (49 men *vs.* 31 women) were included. Their mean age at the time AH occurred was 49±16 (range, 13–86) years; 14/74 (18.9%; 6 missing data) patients were smokers and 3 (3.8%) had congestive heart failure at the time of AH. AAV were distributed as follows: 49 (61.3%) GPA (Wegener) cases, followed by 21 (26.3%) MPA, 8 (10%) CSS and 2 (2.5%) unclassified patients, in whom small-vessel vasculitis of the lung or kidney was histologically confirmed. ANCA were detected in 71/77 (92.2%) patients (3 missing data) (46/49 (93.9%) GPA (Wegener)), 21/21 (100%) MPA, 4/7 (57.1%) CSS (1 missing data) and 0/2 unclassified vasculitis. Anti-glomerular basement membrane antibodies were detected concomitantly in 2 patients (1 each with anti-proteinase-3 or -myeloperoxidase antibodies).

Haemoptysis as the first manifestation of vasculitis and severity

Seventy-seven (96.3%) patients had experienced haemoptysis or AH of various abundance as the first, or one of the first manifestations leading to vasculitis diagnosis: during the week before diagnosis for 20 (25%), within the preceding month for 13 (16.3%), 1–3 months prior to diagnosis for 12 (15%), 4–6 months before for 7 (8.8%) and 6 months to ≥1 year for 8 (10%), with no precise times established for 17 (21.3%). For 7 patients, haemoptysis remained of unknown origin ≥1 year before AAV diagnosis (range, 13–49 months). For 3 patients, when bleeding occurred was not precisely known. Twenty-five (31.2%) patients had AH-associated hypoxia. These severe AH occurred in 21/25 patients within the 6 months preceding AAV diagnosis. Haemoglobin concentration fell >1 g/dl during the 48 hours after AH in 48 (60%) patients. Among the 10 (12.5%) patients (4 GPA (Wegener), 5 MPA and

1 unclassified vasculitis) requiring mechanical ventilation for AH, 3 had experienced their first minor haemoptysis (bloody sputum) 2 during the week and 1 during the month before AH and subsequent vasculitis diagnosis.

X-ray, CT scan and BAL

Chest x-ray and/or CT-scan images consistent with AH were obtained for 68 (85%) patients. Seventy-one (88.7%) patients underwent bronchoscopy and BAL, and AH was confirmed by bloody aspirated fluids, Golde score >20 and/or >20% siderophages seen in BAL cytology in 48/71 (67.6%). BAL was not performed in 9 patients because AAV had been diagnosed by renal biopsy and presence of ANCA. None of these 9 patients had severe AH. Histological examination of lung biopsies from 6 patients found active vasculitis (data not shown).

Concomitant renal insufficiency

Among 61 (76.3%) patients with pulmo-renal syndromes (AH and serum creatinine >140 μmol/L), 37/49 patients had GPA (Wegener) (75.5% of all GPA (Wegener)), 19/21 had MPA (90.4% of all MPA), 3/8 had CSS and 2/2 had unclassified vasculitis. Mean creatininaemia at the time of acute vasculitis was 229±259 mmol/L. Three (37.5%) CSS patients had pulmo-renal syndromes, as did the 2 patients with unclassified vasculitis. Renal biopsies from 54 patients showed active pauci-immune glomerulonephritis in 52 (96.3%); 2 renal biopsy results were not available. Among the 10 patients requiring mechanical ventilation, 6 had pulmo-renal syndromes.

Other AAV symptoms were lung nodules in 12 (GPA (Wegener) only) patients; arthralgias and myalgias in 48; ear, nose and throat in 48 (35 GPA (Wegener), 5 MPA and 8 CSS); eyes in 10 (7 GPA (Wegener), 2 MPA and 1 CSS), and peripheral nervous system in 14. Gastrointestinal, central nervous system and skin involvements were anecdotal.

Outcomes

Mean follow-up was 7.3±13.9 years (range, 1 month to 19 years). One patient was lost-to-follow-up. The initial AH episode was never fatal. Forty-seven (58.8%) patients relapsed: 23 with AH with (13) or without (10) other organ(s) involvement(s), 24 with non-AH manifestation(s) (Table I). Among patients who relapsed with AH, only 3 had severe bleeding requiring intensive care unit admission; 2 of them died of renal failure and infection (creatininemia 544 and 290 mmol/L, respectively), while the third survived with a creatininemia at 190 mmol/L. Thirty patients experienced a second relapse and 5 a third relapse. The majority of patients again responded to treatment.

Three patients received kidney transplants with good renal function. Sixteen (20%) patients died: 8 GPA (Wegener) and 8 MPA. Causes of deaths are detailed in Table I; 14 (87.5%) of them had developed pulmo-renal syndromes. Survivors' mean creatininemia was 208±273 mmol/L at the end of follow-up.

Table I. Relapse and mortality rates for the 80 AAV patients with AH after a mean (±SD) 88±167 months of follow-up.

Event	Patients, n (%)
Relapses	47 (58.8)
Without AH*	24 (30)
Subglottic stenosis	3
Lung nodules	1
Arthralgias	7
Pachymeningitis	1
Renal	5
Ear, nose & throat	9
With AH	23 (28.8)
Alone	10 (12.5)
And other organ involvement*	13
Kidney	7
Arthralgias	7
Ear, nose & throat	6
Skin	5
Eyes	3
Nervous system	4
Gastrointestinal	2
Deaths	16 (20)
Septic shock	3
Cancer†	4
End-stage renal failure	2
Methotrexate toxicity	1
Other	6
Cerebral aneurysm	1
Valve replacement‡	1
Unrelated to vasculitis	1
Unknown	3

*Several symptoms could be present at the time of relapse. †1 bladder cancer, 2 lung cancers, 1 ovarian cancer. ‡The immediate cause of death was cardiac insufficiency.

Timing and choice of treatments

The mean time between AH diagnosis and treatment onset was 5.9 (range, 0–60) days. Treatment of the first AH episode included corticosteroids for every patient, combined with intravenous cyclophosphamide for 66 (82.5%); oral cyclophosphamide for 5, plasma exchanges for 16 and methotrexate for 4. Seventy-three/81 patients received pulse methylprednisolone, 15 mg/kg each day for 3 days. The initial steroid dose was 1 mg/kg/day. Steroids were tapered after 3 to 4 weeks. For relapses, corticosteroids and cyclophosphamide were again given to the majority of patients, with rituximab successfully prescribed to 3. Plasma exchanges were also used in 4 patients with first relapses. Plasma exchange indication was not codified. They were prescribed according to local practice. Six plasma exchanges over 2 weeks were usually prescribed. The patients' Kaplan-Meier survival curve is shown in Figure 1.

Discussion

AH is often considered a severe manifestation of AAV, frequently responsible for death. However, this poor outcome had never been confirmed on large series of patients. Moreover, when analysing the prognostic factors of vasculitis, we never found AH to be associated with an increased number of deaths and, even for the most severe cases, the outcome was not the consequence of AH but that of the concomitant renal insufficiency (6). The objectives of this study on AAV with AH were to describe, for a large AAV population with AH, the time of AH occurrence, clinical vasculitis characteristics, outcomes and treatments. Because this analysis concerned a specific subpopulation of patients recruited based on one of the vasculitis manifestations, its conclusions should not be misconstrued as reflecting characteristics and outcomes of other AAV subpopulations. The objective of this work was not to provide data on the frequency of AH in AAV and to compare patients with and without AH recorded in the database of the FVSG. Prognosis of vasculitides with a special attention on the weight of clinical symptoms has already been

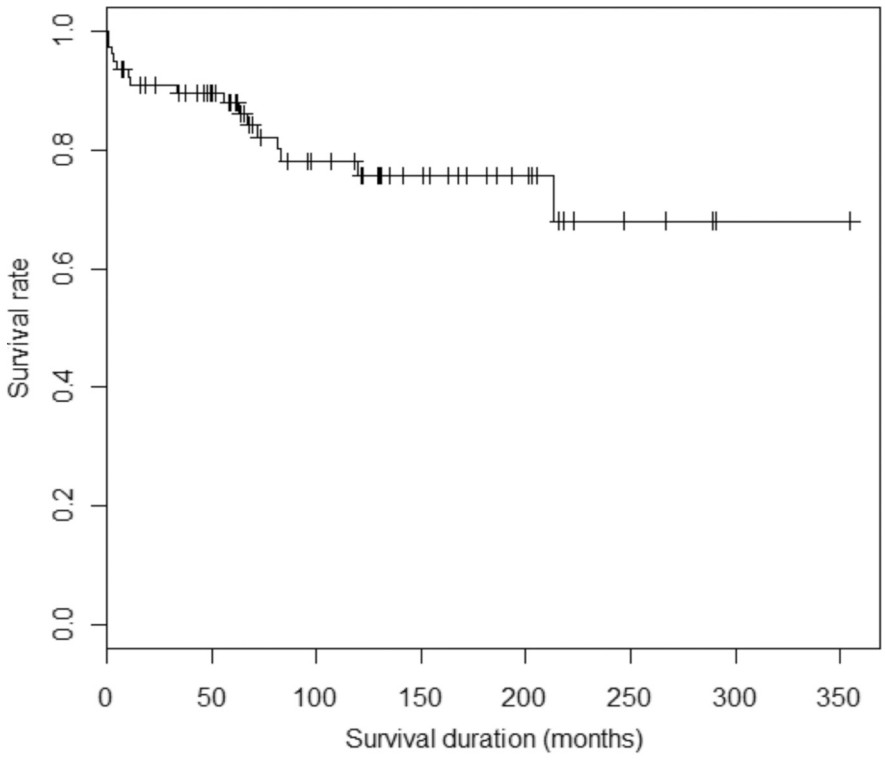

Fig. 1. Kaplan–Meier survival curve for the 80 ANCA-associated vasculitis patients with alveolar haemorrhage as of AAV diagnosis.

published by our group in a recent paper (6). This series of patients did not overlap with the series of patients reported in a previous study (19).

Minor haemoptysis appears to be a reliable early sign of AAV because, in our patient series, bloody sputum or more abundant AH preceded AAV diagnosis. The high frequency of haemoptysis as the first manifestation of AAV shows that this symptom, sometimes considered as minor, should be carefully searched. Indeed, the diagnosis was sometimes not made when haemoptysis occurred but was proven when other symptoms, renal insufficiency or other systemic symptoms, became manifest. We suggest that AH can be underreported or underrecognised. The majority of our patients' AAV were diagnosed because of a pulmo-renal syndrome, with or without renal insufficiency. These observations should draw physicians' attention to the need to investigate carefully patients with bloody sputum or haemoptysis of unknown origin, especially not to restrict themselves to pulmonary manifestations. Our series' diagnoses were often made when new abundant haemoptysis or extrapulmonary manifestations developed. Among our patients requiring mechanical ventilation, 3 experienced minor bloody sputum before AH was diagnosed, meaning that the initial abundance of haemoptysis cannot predict the severity of the next event. In patients with known AAV, investigations are also required to determine whether they reflect a vasculitis relapse or AH of another origin.

Sixty-one patients, the majority with GPA (Wegener) or MPA, experienced AH and had concomitant renal impairment (pulmo-renal syndrome); however, the latter also occurred in CSS and unclassified vasculitis.

During the mean follow-up of 7.3±13.9 years, pulmo-renal syndrome patients had the highest mortality rate. Our overall 20% mortality, lower than the rate reported for other series, might be explained by the heterogeneity of patients studied (10) and our prompt initiation of treatment: immunosuppressants (mainly corticosteroids and intravenous cyclophosphamide) were prescribed as soon as the diagnosis was made. However, the diagnosis was made too late for some patients, because they had experienced minor haemoptysis and other AAV symptoms were absent or unrecognised. In agreement with previous reports (11, 12), AAV relapses occurred in >50% of our patients.

Conventional steroid and cytotoxic therapy (13-16) still seemed to bear heavy responsibility for deaths, with cancer and sepsis accounting for 54% of them. Promising recent (17, 18) and ongoing trials have focused on alternative therapies aimed at inducing sustained remission with fewer short- and long-term side effects, but no definitive data have been reported to date.

The findings of this observational cohort study again confirmed the multivariate analyses that contributed to the creation of the FFS, *i.e.* AH was not a statistically significant poor-prognosis factor because, when it was a life-threatening symptom, it was part of a pulmo-renal syndrome in the majority of patients. Therefore, AH was included within the poor-prognosis renal factor. Furthermore, this study provided additional data supporting the low impact of AH on the overall AAV prognosis, despite its sometimes being a catastrophic event.

Respiratory function after AH was not examined herein. However, it was previously reported that recovery of respiratory function among survivors was considered clinically complete for 69% of the affected patients (19), highlighting that only 30% of the patients had persistently impaired pulmonary function.

Probably one of the most intriguing questions of AAV AH remains its therapeutic management, since no definitive consensus has been reached among different groups. Given its potential severity, patients usually receive a combination of corticosteroids and immunosuppressants, mainly cyclophosphamide, which should be prescribed to the majority of patients with pulmo-renal syndrome. Although intravenous and oral cyclophosphamide have been shown to have similar efficacies against AAV (14, 21-22), for several decades we have preferred the former for AH, given its optimal benefit/risk ratio (14, 20-22). Conversely, in the absence of concomitant poor-prognosis factors

(*e.g.* renal insufficiency), no evidence advocates systematically treating patients with cytotoxic agents, based on AH alone, because AH is not a poor-prognosis factor, *per se*. However, it should be underlined that treatment choice based on FFS is not applicable to GPA, in which immunosuppressants combined to steroids are compulsory. Rituximab is also an alternative to cyclophosphamide to treat AAV (17, 18) even if its indication has not been evaluated prospectively in a population of patients with AH-associated AAV.

Even in the absence of controlled trial support, most specialists recommend plasma exchange to treat AH occurring in Goodpasture's syndrome (20), in which antigen-antibody complexes play a major pathogenic role. By analogy, plasma exchange is often prescribed during the early days of AH (23) but its indication has not been codified according bleeding severity and abundance. However, because the plasma exchange efficacy has now been demonstrated to improve renal function in patients with AAV and creatininaemia >500 µmol/L (24, 25), it seems reasonable to also prescribe them for AAV AH as recommended by Klemmer who showed in a short series of patients (26) that a treatment combining steroids, cyclophosphamide and plasma exchanges was effective without mortality. An ongoing international prospective trial (PEXIVAS) evaluating plasma exchange in a larger population of AAV patients could yield more information on their effectiveness against AH, even though it is not specifically tailored for this purpose.

In conclusion, according to the results obtained herein, isolated AH is not a predictor of AAV poor prognosis. More frequently than in the past, we add plasma exchange (7 sessions in 2 weeks) (25) when bleeding is severe. Outcomes are usually good, as AH is not, in this series of patients, considered a major cause of death of AAV patients when concomittent renal insufficiency is absent.

List of FVSG members who contributed to the study

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