Alveolar hemorrhage in anti-basement membrane antibody disease: A series of 28 cases

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Alveolar Hemorrhage in Anti-Basement Membrane Antibody Disease

A Series of 28 Cases

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Abstract: Anti-basement membrane antibody disease is a rare disorder characterized by the presence of autoantibodies binding to the alveolar and glomerular basement membranes, and mediating both alveolar hemorrhage and acute glomerulonephritis. We retrospectively analyzed 28 cases of anti-basement membrane antibody disease with alveolar hemorrhage proven by bronchoalveolar lavage. The median age of patients at diagnosis was 23 years; 68% were male, 89% were active smokers, and 36% were exposed to some other inhaled agent. At diagnosis, 46% had predominant pulmonary involvement with normal initial serum creatinine. Lung function tests disclosed a restrictive ventilatory defect in 28% (n = 11) and hypoxemia (moderate in 29% and severe in 29%, n = 21). Carbon monoxide transfer factor was elevated in only 25% (n = 12). Bronchoalveolar lavage was more sensitive than any other criterion for detecting alveolar hemorrhage. After onset of treatment, new hemoptysis or transient worsening of hypoxemia occurred in 29% but did not affect pulmonary outcome. In contrast, worsening of renal function occurred in 33% and adversely affected renal outcome. At last follow-up (median, 2.6 yr; n = 24), all patients were alive and a complete cure was achieved in 50%. Long-term dialysis or renal transplantation was required in 42%, and 8% had mild chronic renal insufficiency. Last chest X-ray was normal in all cases, and no patient had respiratory insufficiency. All patients with predominant pulmonary involvement at presentation maintained independent renal function. In summary, this cohort was characterized by frequent exposure to tobacco smoking and other inhaled agents, and a constantly favorable pulmonary outcome contrasting with frequent chronic renal failure. Renal outcome was excellent in the subgroup of patients with predominant pulmonary involvement.

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Abbreviations: AaPO2 = alveolo-arterial oxygen difference, ABMA = anti-basement membrane antibody, AH = alveolar hemorrhage, ANCA = antineutrophil cytoplasmic antibodies, BAL = bronchoalveolar lavage, CO = carbon monoxide, CRP = C-reactive protein, CYC = cyclophosphamide, FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, GERMOP = Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires, HRCT = high-resolution computed tomography, IgG = immunoglobulin G, PaCO2 = arterial carbon dioxide partial pressure, PaO2 = arterial oxygen partial pressure, RV = residual volume, SIOLD = Swiss Group for Interstitial and Orphan Lung Diseases, TLC = total lung capacity, TLCO = carbon monoxide transfer factor, TLCO/VA = carbon monoxide transfer coefficient.

INTRODUCTION

Anti-basement membrane antibody (ABMA) disease is a rare autoimmune disorder characterized by the presence of autoantibodies directed against the carboxyl terminus of the noncollagenous domain of the alpha-3 chain of type IV collagen[64], an epitope primarily located on alveolar and glomerular basement membranes. Binding of ABMAs to their target antigen mediates rapidly progressive crescentic glomerulonephritis and alveolar hemorrhage (AH)[4]. In about half the cases of ABMA disease, AH occurs together with glomerulonephritis[27,50,68]. The remaining half mainly consists of glomerulonephritis without clinically apparent AH[27,50,68], while isolated AH occurs in only 5% of cases[27,50]. The cause of this apparently selective organ involvement is unclear.

Diagnostic criteria of AH were not uniform among reports on ABMA disease. Hemoptysis, alveolar opacities, anemia, hypoxemia, and/or elevated carbon monoxide transfer factor (TLCO) have been used to define AH in previous series, with an incidence of AH varying between 45% and 67%[20,27,43,68]. However, chest opacities and hypoxemia are not specific and may be related to other

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causes, such as fluid overload secondary to renal failure or infection. Hemoptysis, anemia, and especially elevated TLCO are indirect markers of AH of unknown sensitivity and specificity. These limitations in AH definition have prevented a clear view of the impact of AH in ABMA disease. Data on the long-term pulmonary outcome following AH in ABMA disease are also scarce[18].

We therefore analyzed a series of patients with ABMA disease and well-defined AH. The specific objectives were to evaluate the relative impact of pulmonary and renal involvement in ABMA disease with AH, to determine whether subclinical AH may occur, to evaluate the characteristics of predominantly pulmonary forms of the disease, and to determine the long-term pulmonary outcome.

METHODS

Case Recruitment

This retrospective study was undertaken by the French Groupe d'Etudes et de Recherche sur les Maladies Orphelines Pulmonaires (GERMOP) and the Swiss Group for Interstitial and Orphan Lung Diseases (SIOLD). Pulmonary physicians participating in these networks and their corresponding nephrologists were asked to report all cases of rare (so-called orphan) pulmonary diseases to the GERMOP and SIOLD registries, including ABMA disease with AH. For the purpose of this study, physicians who had reported cases of ABMA disease were requested to provide detailed clinical data by reviewing the medical records and completing a questionnaire. The study protocol was approved by the Ethics Committee of the Geneva University Hospitals.

Case Selection

All 3 of the following criteria were required for inclusion: 1) ABMA disease defined by the presence of ABMA in serum, or as linear immunoglobulin G (IgG) deposits along glomerular or alveolar basement membranes by immunofluorescence of renal or lung biopsy; 2) AH defined by 1 of the following: a) macroscopically pink or red bronchoalveolar lavage (BAL) fluid, or b) Golde score of BAL fluid >100, or c) histologic diagnosis of AH by open lung biopsy; and 3) absence of alternative established cause of AH. The presence of hemoptysis, anemia, or chest opacities, either alone or in combination, were not sufficient for inclusion. ABMAs were considered to be present in peripheral blood when the titer exceeded the normal value of the local laboratory.

Data Analysis

Initial room air alveolo-arterial oxygen difference (AaPO2) was used as the main indicator of the severity of pulmonary involvement at presentation. AaPO2 was estimated using the simplified alveolar gas equation, where AaPO2 = 0.21 (760 − 47) − (PaCO2/0.8) − PaO2 (mm Hg). Estimation of the severity of renal involvement at presentation was based on initial serum creatinine. For each of these 2 markers of disease severity, relationships were investigated with the following explanatory variables: age, sex, history of smoking, number of pack-years smoked, history of inhaled agents, time from first symptoms to diagnosis, initial hemoglobin (reflecting the severity of alveolar bleeding), initial C-reactive protein (CRP), initial serum creatinine level, and initial AaPO2. Last available AaPO2, lung function, and chest X-ray were used as indicators of long-term pulmonary outcome. Long-term dialysis and renal transplantation were used as indicators of poor long-term renal outcome under the term ''renal death.'' The following treatment characteristics were analyzed as 1) possible dependent variables of initial disease severity, and 2) possible determinants of final outcome: number and dose of intravenous corticosteroid pulses, initial dose and total duration of oral corticosteroids, use of immunosuppressive agents, number and dose of intravenous cyclophosphamide (CYC) pulses, dose and duration of oral CYC treatment, use of plasma exchange, number of plasma exchanges, duration of plasma exchange therapy, dialysis during the acute phase, long-term dialysis, and renal transplantation. Results are expressed as median (range). Continuous variables between 2 groups were compared by the Mann-Whitney test. Correlations between 2 continuous variables were analyzed by the Spearman rank test. Proportions were analyzed by the chi-square test and the Fisher exact test. Abbreviations of lung function parameters are detailed in Table 3.

RESULTS

Study Population

Thirty-seven questionnaires were available for analysis. Nine cases were excluded for 1) absence of BAL or lung biopsy demonstrating AH, despite presence of hemoptysis and/or opacities at chest imaging (n = 8), and 2) alternative cause of AH (infectious pneumonia and anticoagulant therapy, n = 1). The remaining 28 cases were included. The diagnosis of ABMA disease was established by detection of ABMA in the peripheral blood (n = 18, 64%), and/or as linear IgG deposits along glomerular (n = 23, 82%), and/or alveolar (n = 4, 14%) basement membranes. AH was diagnosed by the presence of macroscopically pink or red BAL fluid (n = 27, 96%), and/or a Golde score >100 (n = 10, 36%), and/or AH on open lung biopsy (n = 5, 18%).

Baseline Patient Characteristics

The diagnoses were made between 1983 and 2003 (median, 1998), without seasonal predominance. Male patients were twice as numerous as females (68% vs. 32%; p = 0.02). The median age at diagnosis was 23 years (range, 17–65 yr), with 54% of patients aged 20–30 years, and 21% aged 30–40 years. Most patients were active smokers (89%), with a median of 5 pack-years (range, 2–40 pack-years), and without significant difference between the sexes. Besides tobacco smoking, a history of exposure to vapor or fumes was found in 36%, including 25% with a clear recent respiratory exposure to 1 or more of the following: cocaine (n = 4), marijuana (n = 3), heroin (n = 1), diesel fumes (n = 1), insecticides (n = 1), and tear gas (n = 1). Another

11% had a possible inhalation exposure, in the form of occupational exposure to water vapor in a professional cook with recurrent hemoptysis on reexposure (n = 1), work in a tannery (n = 1), and a history of hemoptysis triggered by inhalation of a detergent 2 years earlier (n = 1). Altogether, only 7% of patients did not have any history of exposure to an inhaled agent. A previous autoimmune disease was found in 2 patients, consisting of cutaneous leukocytoclastic vasculitis attributed to a drug reaction 2 months earlier (n = 1), and Henoch-Schönlein purpura 29 years earlier at the age of 5 years (n = 1). Another patient developed Sjögren syndrome 9 years after the occurrence of ABMA disease. No patient had a history of recent immunization. A recent upper airway infection was reported in 18%, and 1 patient had recently documented infectious mononucleosis.

In 57% of cases, symptoms developed subacutely between 1 week and 1 month before hospital admission. In another 39%, symptoms developed more progressively over more than a month. Acute symptoms leading to hospitalization in less than 1 week were uncommon (4%). The median delay from first symptoms to diagnosis was 5 weeks (range, 2–126 wk), and the median delay from hospitalization to diagnosis was 6 days (range, 0–53 d).

Clinical Features

The clinical features at presentation are summarized in Table 1. Among general symptoms, only fatigue was a common feature seen in about two-thirds of patients, whereas a minority had fever (43%), weight loss (18%, with a median loss of 4 kg; range, 2–8 kg), arthralgia (18%), and myalgia (18%). The most common respiratory symptoms were dyspnea (79%), hemoptysis (75%), and cough (64%).

TABLE 1. Baseline Patient Characteristics at Diagnosis (n = 28)

Characteristic	%
General manifestations	
Fatigue	64
Fever	43
Flu-like illness	32
Nausea or vomiting	25
Weight loss	18
Arthralgia	18
Myalgia	18
Respiratory manifestations	
Dyspnea	79
Hemoptysis	75
Cough	64
Crackles at auscultation	50
Chest pain	14
Renal manifestations	
Macroscopic hematuria	36
Edema	32
Anuria >24 h	18

In 19 evaluable cases, the New York Heart Association functional class disclosed class I dyspnea in 16%, class II in 37%, class III in 21%, and class IV in 26%. Chest pain was uncommon (14%). Crackles were heard on admission in half the patients, and chest auscultation was unremarkable in the other half.

Laboratory and Immunologic Data

Laboratory data on admission are summarized in Table 2. Moderate to severe anemia (hemoglobin <110 g/L) was present in 78%, with a median hemoglobin value of 96 g/L, and a median hematocrit of 29%. The median values of blood leukocytes and CRP were in the upper normal range. Fifty-four percent of cases had elevated serum creatinine (>120 μmol/L), but a creatinine level >500 μmol/L was found in only 20% of patients. No relationship was found between initial creatinine and, respectively, age, time from first symptoms to diagnosis, initial hemoglobin,

TABLE 2. Laboratory and Immunologic Data on Admission

	n	Median Value or Frequency	Range
Hematology			
Hemoglobin, g/L	28	96.0	50–146
Hematocrit, %	28	29.0	17–42
Blood leukocytes, G/L	26	9.6	5.7–29.9
Neutrophils, G/L	23	5.4	2.4–23.9
Lymphocytes, G/L	23	2.0	1.1–5.1
Eosinophils, G/L	23	0.2	0–0.9
Platelets, G/L	26	343.0	52–652
C-reactive protein, mg/dL	18	7.0	2–463
Renal function			
Serum creatinine, μmol/L	25	112.0	54–1898
Proteinuria, g/d	20	1.2	0–35
Proteinuria >0.3 g/d, %	20	70.0	NA
Microscopic hematuria, %	28	79.0	NA
Leukocyturia, %	24	46.0	NA
Red blood cell casts, %	16	38.0	NA
Immunology			
Circulating ABMA, %	28	64.0	NA
Tissular ABMA, %	27	100.0	NA
Positive IF on kidney biopsy, %	23	100.0	NA
Positive IF on lung biopsy, %	4	100.0	NA
p-ANCA*, %	27	7.0	NA
Antinuclear antibodies, %	28	7.0	NA

Abbreviations: NA = not applicable, IF = immunofluorescence, p-ANCA = antineutrophil cytoplasmic autoantibodies with perinuclear distribution.

*Of the 2 patients with p-ANCA, 1 had documented recent infectious mononucleosis, arthralgia, myalgia, creatinine 122 μmol/L, proteinuria 1.25 g/d, and p-ANCA titer of 1/50 by IF (anti-myeloperoxidase specificity not available). The second patient had arthralgia, myalgia, headache, creatinine 778 μmol/L, proteinuria 1.6 g/d, CRP 463 mg/dL, and p-ANCA with anti-myeloperoxidase specificity at 33 UI/L.

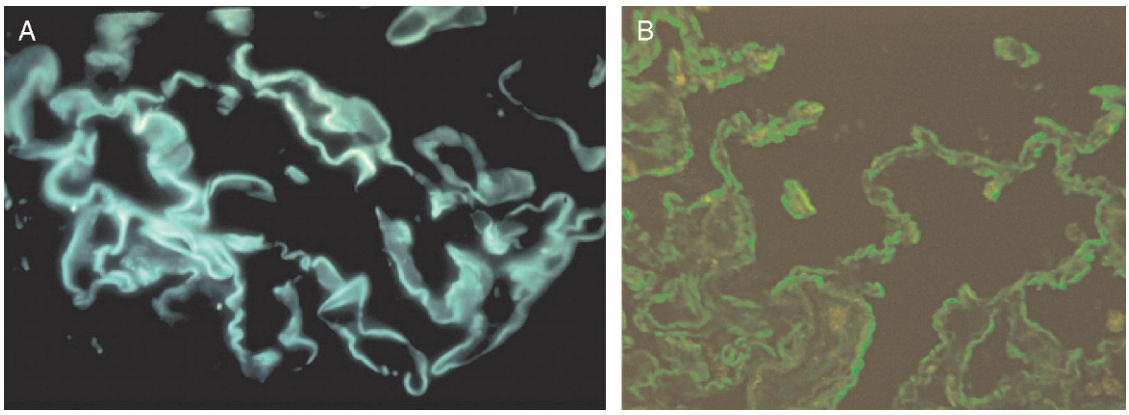

FIGURE 1. Diagnosis of anti-basement membrane antibody disease by immunofluorescence. **A.** Renal biopsy: staining with fluorescein-marked anti-IgG antibodies reveals linear IgG deposition along glomerular basement membranes. The focal discontinuity of the linear stain reflects sites of glomerular basement membrane rupture. **B.** Open lung biopsy: fluorescence stain reveals IgG deposits along alveolar basement membranes. Open lung biopsy is only rarely needed for the diagnosis of ABMA disease.

initial CRP, and initial AaPO2. Patients with a history of vapor/fumes exposure had significantly lower initial serum creatinine (n = 8; median, 71 μmol/L; range, 54–136 μmol/L) compared with those without exposure (n = 17; median, 227 μmol/L; range, 76-1898 μmol/L; p = 0.001).

A worsening of renal parameters between hospital admission and onset of treatment occurred in 4 of 10 evaluable patients over a median delay of 10 days (range, 2–46 d), with an increase of serum creatinine in 3 patients, and the appearance of hematuria in 1.

Circulating ABMAs were found in two-thirds of the patients (see Table 2). A kidney biopsy was performed in 25 patients, and linear IgG deposits along glomerular basement membranes were found in all 23 patients with available immunofluorescence data (Figure 1A). Similarly, a lung biopsy was performed in 5 patients, and linear IgG deposits along alveolar basement membranes were detected in all 4 patients in whom they were sought (Figure 1B). Circulating perinuclear antineutrophil cytoplasmic antibodies (ANCA) were found in 2 patients (7%) with no other features suggestive of vasculitis.

Lung Function Tests

Initial lung function tests (Table 3) were performed at a median time interval of 11 days before diagnosis (range, 50 d before to 16 d after). A mild restrictive ventilatory defect,

TABLE 3. Initial Lung Function

				Frequency of Abnormal Values	
	n	Median	Range	Criterion	Rate (%)
FEV1, %pred	10	83	70–106	<80	40
FVC, %pred	10	83	77–99	<80	40
FEV1/FVC, %	10	79	70–94	<70	0
TLC, %pred	11	92	75–106	<80	27
RV, %pred	11	103	62–189	<80	18
RV/TLC, %pred	11	124	91–180	>120	55
TLCO, %pred	12	77	60–179	>120	25
				<80	50
TLCO/VA, %pred	9	97	78–201	>120	22
				<80	22
PaO2, mm Hg	21	72	38–110	<80	58
PaCO2, mm Hg	20	33	20–44	<35	52
AaPO2, mm Hg	20	33	0–67	≥20	65

Abbreviations: FEV1 = forced expiratory volume in 1 second, FVC = forced vital capacity, TLC = total lung capacity, RV = residual volume, TLCO = carbon monoxide transfer factor corrected for hemoglobin, TLCO/VA = carbon monoxide transfer coefficient corrected for hemoglobin, PaO2 = arterial oxygen partial pressure, PaCO2 = arterial carbon dioxide partial pressure, AaPO2 = alveolo-arterial oxygen difference.

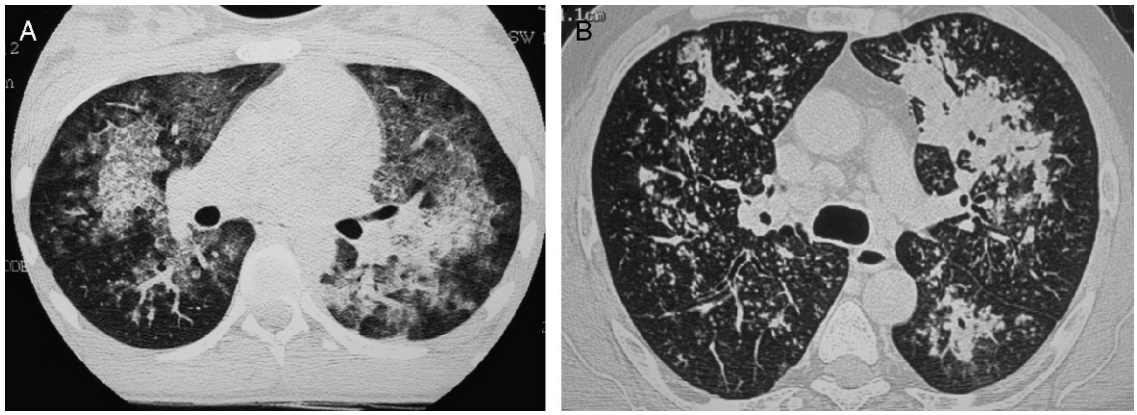

FIGURE 2. High-resolution computed tomography of alveolar hemorrhage in anti-basement membrane antibody disease. **A.** Diffuse ground-glass opacities of varied density, and areas of consolidation with air bronchogram. **B.** Patchy parenchymal consolidation with air bronchogram, and an uncommon micronodular pattern with areas of confluency.

defined as TLC <80% predicted, was found in 3 of 11 patients (27%) with available data. Among 10 patients with available spirometry, none had an obstructive ventilatory defect defined by a forced expiratory volume/forced vital capacity ratio (FEV1/FVC) <70%. Air trapping (RV/TLC >120% predicted) was found in 6 of 11 patients (55%), all active smokers with a median of 10 pack-years (range, 2–25 pack-years).

TLCO was elevated >120% predicted in only 3 of 12 patients (25%). Moderate hypoxemia (PaO2 between 60 and 80 mm Hg) was present in 29% of patients, and severe hypoxemia (PaO2 <60 mm Hg) was found in 29%. AaPO2 >20 mm Hg was found in 65%. No significant relationship was found between initial AaPO2 and any baseline characteristic.

Chest Imaging

On chest X-ray (n = 28), abnormalities were present in only 86% of patients. The upper lung fields were involved in 46% and the lower lung fields in 68%. The most frequent abnormalities were consolidation (43%) and ground-glass opacities (39%). Nodules were uncommon (11%). On high-resolution computed tomography (HRCT) (n = 20), abnormalities were present in only 80% of patients. The upper and lower lung fields were respectively involved in 35% and 50% of cases. Ground-glass opacities were found in 55% of cases, consolidation in 40%, and nodules in 20%. Figure 2 shows HRCT patterns of ground-glass, consolidation, and nodules in 2 patients with AH.

BAL and Lung Biopsy

BAL was performed in all 28 patients. Twenty-seven patients had macroscopically pink or red BAL, and 1 patient for whom this information was missing had a Golde score >100. Microscopic BAL fluid analyses were available in 25 patients (Table 4). An increased number of hemosiderin-laden macrophages >30% was found in 92%, and an elevated Golde score >100 was present in 90% of evaluable cases. Among the 19 available differential counts, only 16% were entirely normal, whereas 84% had increased neutrophils. In 2 patients, who underwent a second BAL 3 and 5 months after the acute phase, the Golde score remained elevated (229 and 173, respectively).

Lung biopsy was performed in 5 patients with normal creatinine. All had a macroscopically hemorrhagic BAL. Lung immunofluorescence was positive for IgG in all 4 cases

TABLE 4. Bronchoalveolar Lavage (n = 25)

				Frequency Of Abnormal Values	
	n	Median	Range	Criterion	Rate (%)
Differential cell count					
Macrophages, %	19	66	2–97	≤90	84
Neutrophils, %	19	22	1–90	≥5	84
Lymphocytes, %	19	4	0–30	≥12	16
Eosinophils, %	19	0	0–7	≥5	11
Analysis of iron in macrophages					
Hemosiderin-laden macrophages, %	12	74	5–100	≥30	92
Golde score	10	160	63–350	≥100	90

with available data, but in only 1 case did it provide critical evidence of ABMA disease, since all others had ABMA in peripheral blood or renal biopsy. Lung histopathology showed diffuse or multifocal AH with numerous red blood cells and/or hemosiderin-laden macrophages in alveolar spaces. One patient also had sparse foci of alveolar wall disruption and minimal neutrophilic infiltration consistent with capillaritis.

Treatment

Detailed data on initial treatment were available for 27 patients. All but 2 patients (93%) received intravenous pulse methylprednisolone, with a median number of 3 pulses (range, 3–7 pulses), and a median dose of 13 mg/kg per day (range, 7–15 mg/kg per day). Oral corticosteroids were used in all but 1 case (96%) at a median initial dose of prednisone of 1 mg/kg per day (range, 0.5–2.0 mg/kg per day). Prednisone treatment was continued for a median of 7 months (range, 4–73 mo). One patient did not receive any treatment (a 23-year-old woman presenting with normal renal function, hemorrhagic BAL, a Golde score of 180, pulmonary opacities, no circulating ABMAs but positive ABMAs at open lung biopsy).

Intravenous pulses of CYC were administered in 9 of 27 patients (33%), with a median number of 6 pulses (range, 1–11 pulses), a median dose of 14 mg/kg per pulse (range, 7–19 mg/kg per pulse), and a median time interval between pulses of 4 weeks (range, 2–4 wk). In this subgroup of 9 patients, intravenous CYC was followed by oral CYC in 5 patients, oral mycophenolate mofetil then azathioprine in 1, or no further immunosuppressive agent in 3 patients. Oral CYC was used in 63% of all 27 patients at a median dose of 2 mg/kg per day (range, 1.0–2.5 mg/kg per day) and for a median duration of 3 months (range, 2–26 mo). Azathioprine was used in 3 patients (11%) and mycophenolate mofetil in 1 (4%), either after oral CYC or as single agent. Cumulatively, an immunosuppressive agent was used in 85% of all 27 patients, and the median duration of immunosuppressive therapy was 5 months (range, 2–26 mo). No significant relationship was found between initial values of creatinine and AaPO2 and, respectively, dose and duration of intravenous or oral corticosteroids, as well as dose and duration of intravenous or oral immunosuppressive agents (data not shown).

Seventy-eight percent of patients underwent plasma exchanges, which started a median of 4 days after the diagnosis (range, 0–31 d). The median number of plasma exchanges was 10 (range, 1–25 exchanges), with a time interval between exchanges of 2 days (range, 1–9 d). Patients treated with plasma exchanges had a higher initial serum creatinine level (median, 207 μmol/L; range, 54–1898 μmol/L) compared with others (median, 87 μmol/L; range, 65–112 μmol/L; $p = 0.03$). Initial AaPO2 was not correlated with any characteristic of plasma exchanges (data not shown). Altogether, 70% of patients received a combination of corticosteroids, immunosuppressive agents, and plasma exchanges.

Hemodialysis was required at the time of diagnosis in 11 patients (41%). Initial AaPO2 was similar in dialyzed and nondialyzed patients (p = not significant). Only 3 patients (11%) required mechanical ventilation, for a median duration of 3 days (range, 2–4 d). Blood transfusions were needed in 59%.

One or more treatment side effects occurred in 42% of patients, consisting of amyotrophy (n = 1), edema (n = 2), diabetes (n = 1), oral mycosis (n = 1), skin rash (n = 3), lymphangitis (n = 1), anemia (n = 1), leukopenia (n = 1), hemorrhagic cystitis (n = 1), infectious spondylodiscitis (n = 1), dilated cardiomyopathy attributed to CYC toxicity (n = 1), and azoospermia (n = 1).

To determine whether changes in treatment modalities occurred over time, we compared cases treated during the first decade (1983–1993, n = 7) with those treated during the second decade (1994–2003, n = 20) for all treatment characteristics. Only the frequency of use of intravenous CYC was higher during the second decade (45% vs. 0%; $p = 0.03$); no statistically significant difference was found for all other parameters.

Clinical Course and Outcome

A follow-up of >3 months was available for 24 patients, with a median duration of 2.6 years (range, 0.4–17.6 yr). Data are summarized in Table 5. ABMAs disappeared in all 15 cases with available data.

Pulmonary worsening after onset of treatment occurred in 7 patients (29%). Reappearance of hemoptysis and/or pulmonary opacities were observed in 5 patients, after a median delay of 10 months (range, 0.1–54.0 mo), and with up to 7 hemoptysis episodes (median, 1 episode). One of these patients also had worsening of renal function. Worsening of hypoxemia without hemoptysis occurred in 2 patients 1 and 2 months, respectively, after treatment onset, and paralleled worsening of renal function. These 7 patients with pulmonary worsening had lower initial creatinine levels than those without worsening (median, 76 vs. 217 μmol/L; $p = 0.04$), but were otherwise similar for all characteristics, including all initial treatment modalities (data not shown). None had ANCA. No relationship was found between

TABLE 5. Clinical Course and Outcome* (n = 24)

Worsening after treatment onset	
Renal, %	33
Pulmonary, %	29
Renal and pulmonary, %	13
Renal or pulmonary, %	50
Time after initial diagnosis, mo (range)	4 (0.1–54.0)
Re-treatment, %	21
Final outcome	
Complete cure without sequelae, %	50
Mild chronic renal insufficiency, %	8
Renal death†, %	42
Chronic respiratory insufficiency	0
Patient death, %	0

*Follow-up >3 mo.
†Chronic dialysis or renal transplantation.

pulmonary worsening after treatment onset and persistent active smoking.

Worsening of renal function after treatment onset occurred in 8 patients, of whom 3 also had pulmonary manifestations. Their median initial creatinine was 229 μmol/L (range, 66-530 μmol/L). Six of them required dialysis during the acute phase, and all progressed to renal death without recovery of independent renal function. None had ANCA. Two other patients had normal initial serum creatinine, but developed renal insufficiency respectively less than 1 week and 2 months after treatment onset. Both retained independent renal function with mild elevation of serum creatinine at last follow-up (110 and 137 μmol/L, respectively). No correlation was found between the occurrence of renal worsening and any explanatory variable in this subgroup, including all initial treatment characteristics and persistent active smoking (data not shown).

Altogether, 12 patients (50%) experienced pulmonary and/or renal worsening after treatment onset. In 5 of these cases (21%), the worsening required increasing or resuming of corticosteroids, either alone or in combination with an immunosuppressive agent.

At last follow-up visit, 17% of patients still received prednisone, at a median dose of 8 mg/d (range, 4–15 mg/d) and a median delay of 10 months after diagnosis (range, 5–22 mo). Eight percent received immunosuppressive agents. Fifty percent continued to smoke. A complete recovery of renal function was achieved in 50% of patients. The other 50% had some form of renal sequelae, consisting of renal death (42%), or mild renal insufficiency (8%). Among the 11 patients who required dialysis during the acute phase, all but 1 (91%) evolved to renal death. The only patient who could be weaned from dialysis eventually developed renal insufficiency 7 years later and required dialysis again, in the absence of ABMA disease recurrence at renal biopsy. The patients who ultimately evolved to renal death were characterized by higher initial creatinine at presentation (median, 486 μmol/L; range, 207–1898 μmol/L), compared with those who retained independent renal function at last follow-up (median, 87 μmol/L, range, 54–511 μmol/L; $p = 0.0002$). No other correlation was found between occurrence of renal death and any baseline or treatment characteristics, as well as persistent active smoking (data not shown). No difference in renal outcome was found between the periods 1983–1993 and 1994–2003. Of the 2 patients with positive p-ANCA at presentation, 1 evolved to renal death with disappearance of all autoantibodies (the other was lost to follow-up). No patient died in this series.

Last available lung function tests, performed after a median delay of 11 months after diagnosis (range, 0.2–118.0 mo), are shown in Table 6. A mild restrictive ventilatory defect was found in 20%, and a mild obstructive ventilatory defect in 10%. The RV/TLC ratio was elevated in 3 of 10 patients (30%) despite a normal FEV1/FVC ratio. Among the 6 patients with initially elevated RV/TLC ratio, 2 had persistent air trapping at follow-up (smoking histories of 3 and 20 pack-years, respectively), whereas 2 others normalized the RV/TLC ratio (smoking histories of 2 and 25 pack-years, respectively). Follow-up RV/TLC was not available in the 2 remaining cases. TLCO and carbon monoxide transfer coefficient (TLCO/VA) were moderately reduced in about one-third of cases. No correlation was found between any baseline characteristic and, respectively, last FEV1, last TLCO/VA, and last AaPO2 (data not shown). No impairment of lung volumes or gas exchange parameters was observed in patients who experienced pulmonary worsening after treatment onset. The last chest X-ray was normal in all 24 cases.

Subgroup With Predominant Pulmonary Involvement

Thirteen patients (46%) had normal initial serum creatinine levels and could be considered as having predominantly pulmonary forms of ABMA disease. Among them, 10 had proteinuria >0.3 g/d and/or microscopic hematuria. In these patients, ABMAs were found either in

TABLE 6. Lung Function at Last Visit

				Frequency Of Abnormal Values	
	n	**Median**	**Range**	**Criterion**	**Rate (%)**
FEV1, %pred	10	91	61–109	<80	20
FVC, %pred	10	96	67–107	<80	20
FEV1/FVC, %	10	80	62–90	<70	10
TLC, %pred	10	100	75–116	<80	20
RV, %pred	10	103	62–169	<80	20
RV/TLC, %pred	10	105	69–146	>120	30
TLCO, %pred	11	80	48–102	<80	45
TLCO/VA, %pred	11	80	57–110	<80	36
PaO2, mm Hg	8	88	82–98	<80	0
PaCO2, mm Hg	8	37	25–43	<35	38
AaPO2, mm Hg	8	18	0–25	≥20	38

Abbreviations: See Table 3.

blood (n = 8), renal biopsy (n = 6), and/or pulmonary biopsy (n = 1). Three patients (11%) had neither proteinuria nor microscopic hematuria. In these, ABMAs were found respectively at lung biopsy (n = 2), and in blood and at renal biopsy (n = 1).

Compared with the patients with initial acute renal failure, the subgroup with normal initial creatinine level was characterized by a longer time interval from first symptoms to diagnosis (median, 8 vs. 4 wk; p = 0.02), and lower proteinuria (0.09 vs. 0.78 g/d; p = 0.02). These patients received lower methylprednisolone pulse doses (8.8 vs. 14.9 mg/kg per bolus; $p < 0.05$), and had a lower rate of plasma exchanges (54% vs. 100%; p = 0.01), a lower need for dialysis (0% vs. 79%; p = 0.0002), and a lower rate of eventual renal death (0% vs. 83%; p = 0.0002). The 2 subgroups were otherwise similar for all baseline characteristics, lung function variables, treatments, and outcome parameters. The patient who did not receive any therapy was doing well with no symptoms, normal renal function, and normal chest imaging at 2.6 years after the diagnosis.

DISCUSSION

To our knowledge, the current retrospective study of ABMA disease with AH is the first to use an unequivocal definition of AH based on BAL or lung biopsy, and to provide a detailed and long-term analysis of lung involvement in this disorder. Cases were mainly recruited by pulmonary physicians, in sharp contrast with most previous series from nephrology units with limited pulmonary data available[12,13,20,27,31,48,62,67,68]. The cohort was characterized by a high prevalence of tobacco smoking and exposure to other inhaled agents, frequently normal initial renal function, frequent pulmonary or renal worsening after onset of treatment, 100% survival, favorable long-term pulmonary outcome in all cases contrasting with a frequent loss of independent renal function, and excellent renal outcome in patients with predominant pulmonary involvement.

Case Selection

In the current study with AH confirmed by BAL in all cases, hemoptysis was present in only 75%, chest opacities in 86%, hypoxemia in 57%, and increased TLCO in only 25%. This clearly shows that BAL is more sensitive than any of these clinical markers for detecting AH in ABMA disease, and could be considered the gold standard. In previous large series of ABMA disease where AH was defined using hemoptysis, anemia, chest opacities, hypoxemia, and/or increased TLCO[12,20,27,43,50,68], the frequency of AH varied from 45%[27] to 67%[20,43]. The current series does not provide any information on the frequency of pulmonary involvement in ABMA disease, since AH was present in all cases by study design.

Patient Characteristics at Presentation

Distribution of sex and age at disease onset was similar to that of previous series[4,20,50]. One striking feature was the high prevalence of active smoking (89% compared to 50%–78% in previous series)[18,21,27]. Although contradictory data exist[20], previous studies have suggested an association between pulmonary involvement in ABMA disease and active smoking[21,27,56]. In 2 series, AH was respectively present in 100% and 91% of smokers but in only 20% and 27% of nonsmokers[21,56]. In another study, the proportion of smokers was 72% and the occurrence of pulmonary involvement was significantly associated with smoking[27]. The high proportion of smokers in the present study further supports an association between smoking and AH in ABMA disease.

Of note, one-third of our patients had some form of exposure to another inhaled agent. Chemical compounds[52], cocaine[25], marijuana[8], hard metal dusts[41], fire smoke[36], and various forms of hydrocarbons[5,6,9,34,37,38] have been associated with AH in ABMA disease. It has been suggested that such agents may damage the capillary endothelium and thus allow circulating ABMAs to reach the alveolar basement membranes, whereas such access is normally prevented by the nonfenestrated pulmonary endothelium[22,30,69]. This hypothesis is supported by data from animal models of ABMA disease produced by the administration of exogenous species-specific ABMA[22,30,69]. In 1 such experiment, intratracheal gasoline instillation induced extravascular pulmonary leakage of radiolabeled albumin and ABMA binding to alveolar basement membranes detected by immunofluorescence[69]. Similar findings were reported with endothelial injury produced by 100% oxygen[22,30]. In human ABMA disease, hydrocarbon exposure was identified in only 6% of >700 reported cases[60]. However, our data suggest that various inhaled agents may be involved as cofactors. Furthermore, patients exposed to an inhaled agent had significantly lower initial creatinine, suggesting that such exposure may locally trigger AH and thus reveal ABMA disease at an early stage, before development of renal failure.

Cocaine inhalation, found in 14% of our cases, deserves a special comment. This agent has been previously associated with the occurrence of ABMA disease[25]. However, cocaine per se is a known cause of AH, even in the absence of renal disease[3,24,53]. Thus, cocaine may be both an independent causal agent of AH and a trigger of AH in ABMA disease. Consequently, ABMA disease with renal involvement should be looked for systematically in patients presenting with AH after cocaine inhalation.

Clinical features at presentation were similar to previous data[20,31,50,62]. Fatigue was the only frequent general symptom, while fever, weight loss, and arthralgia were uncommon, in contrast to AH related to microscopic polyangiitis, a vasculitic pulmonary-renal syndrome[40].

Laboratory and Immunologic Findings

Since anemia in ABMA disease results from blood leakage into alveolar spaces, one would expect a correlation between severity of anemia and severity of gas exchange impairment. However, no relationship was found between initial hemoglobin and initial AaPO2. Gas exchange impairment may be influenced by various factors such as alveolar blood spillage and clearance, capillary permeability,

and extracellular fluid volume. Leukocytes and CRP were elevated in isolated cases, but median values were within the normal range, showing that systemic inflammation is not a feature of ABMA disease.

Forty-six percent of patients in the current study presented with normal serum creatinine, whereas this rate did not exceed 23% in most previous series[12,20,27,50,67,68]. Similarly, a creatinine level >500 μmol/L was found in only 20% in the current study, compared to 70% in some series[43,67]. Our recruitment from pulmonary physicians explains this difference and identifies a subgroup of patients with predominant pulmonary involvement, as discussed below.

Circulating ABMAs were found in only 64% of our patients, compared with 76%[27] to 100%[50] in previous large series[20,27,48,50,62]. This difference may be due to interlaboratory variability or to a lesser sensitivity of immunofluorescence tests used in older cases, although contemporary enzyme-linked immunosorbent assays and immunoblot techniques may also fail to detect circulating antibodies in ABMA disease[59]. Alternatively, the lower positivity of ABMA in the current series likely may reflect an average milder and/or earlier disease stage, with a lesser build-up of the autoimmune process. Importantly, our data confirm that the absence of circulating ABMA does not rule out ABMA disease, and underlines the value of renal biopsy even in the absence of overt renal disease if this diagnosis is suspected.

Perinuclear ANCA were found in 7% of our patients, similar to the 3%–5% reported in previous clinical series[20,27]. Higher rates of 21%–32% were found among patients with circulating ABMA recruited through serum banks[12,29,61,67]. ANCA were usually of the perinuclear type with anti-myeloperoxidase specificity[12,67]. The presence of ANCA has been associated with a worse[10,29], better[12], or similar prognosis[67] in ABMA disease, and ANCA-associated vasculitis has been reported as preceding[66], following[10,55,65], or accompanying ABMA disease[10,12,32,54]. In the current series, the small number of ANCA-positive cases precluded any analysis of the prognostic significance. As previously recommended, ANCA should be looked for in all cases of ABMA disease at initial screening and during follow-up[61].

Pulmonary Function

Lung function during the acute phase was characterized by a moderate restrictive ventilatory defect, but its severity in the whole cohort is certainly underestimated, since patients with the most severe respiratory impairment could not undergo pulmonary function testing. No obstructive ventilatory defect was observed, but an elevated RV/TLC ratio reflecting air trapping was present in 55% (discussed below). AaPO2 was the most common indicator of lung function impairment in our cohort, and was abnormal in two-thirds of cases. The median TLCO was only moderately reduced, as previously observed[31]. Importantly, an elevation of TLCO or TLCO/VA was found in only one-quarter of patients initially, demonstrating that these variables are neither sensitive nor specific diagnostic markers of AH, in contrast to previous observations[1,4,14,56]. Although AH may increase TLCO through CO binding to alveolar hemoglobin, it may simultaneously impair gas transfer from alveolar air to pulmonary capillaries. These opposed effects may result in a relatively normal TLCO.

Chest Imaging

Bilateral alveolar opacities ranging in density from ground-glass to consolidation were a common finding in the current series, similarly to previous reports[62]. However, several patients had normal chest X-rays and even HRCT initially. Relying solely on the presence of opacities at chest imaging may thus lead to underdiagnosis of AH. Some cases previously referred to as purely renal forms of AH based on normal chest imaging may in fact have included undiagnosed AH. One noteworthy feature at imaging was the presence of nodular opacities in around 20% of cases, most likely reflecting areas of focal intra-acinar or intralobular bleeding. This imaging pattern is less well known than the diffuse alveolar pattern, and may be confusing.

BAL and Lung Biopsy

BAL was more sensitive than indirect clinical indicators to diagnose AH. We note that hemosiderin-laden macrophages were still detected in 2 BALs remote from the acute phase. It is unclear whether this reflects a low-grade but still active autoimmune process, or persistent damage to alveolo-capillary walls resulting in chronic red blood cell leakage.

Previous data on BAL differential cell counts in ABMA disease are scarce[52,70]. Mean values of 5.3% ± 1.9% neutrophils, 2.6% ± 1.4% eosinophils, and 11.9% ± 5.3% lymphocytes were reported in a series of 5 cases[70]. In another report, 26% neutrophils and 23% lymphocytes were found in 1 patient[52]. The current study expands knowledge on this issue, and shows that AH is associated with neutrophilic alveolitis.

Lung biopsy was performed in 5 patients. However, all of them fulfilled the BAL criteria of AH, and the lung biopsy did not contribute to the diagnosis of AH. Additionally, ABMAs were positive in blood or renal biopsy in 4 patients, and in only 1 case did the lung biopsy provide critical evidence of ABMA disease. Thus, the overall contribution of lung biopsy to the diagnosis of AH and ABMA disease was small in this series.

Treatment

A combination of corticosteroids, immunosuppressive agents, and plasma exchange is used in ABMA disease[44,46,56], and has been shown to reduce morbidity and mortality[44,46,56] compared with historical controls[68]. Plasma exchange has been shown to accelerate the clearance of circulating ABMA[31,45,56]. In the present study, the use of these treatment modalities was similar to previous series[20,50]. Although the combined therapy has been reported to control AH rapidly[43,46,56], the relative effect of each component remains unclear[31,56]. Likewise, the value of each treatment modality on the final renal outcome has not been established, mainly because therapy appears to be a weaker determinant of renal outcome than initial renal function[31,43]. For the same

reason, we could not detect any relationship between treatment and outcome in our cohort. Interestingly, half of our patients with normal initial renal function did not receive plasma exchanges but nevertheless did well, in agreement with previous data suggesting that patients with predominantly pulmonary involvement and preserved renal function do well with or without plasma exchanges[31]. Besides a more frequent use of intravenous CYC in recent cases, no significant change was observed over time in treatment modalities and in final renal outcome. Although our data did not allow us to analyze this issue in detail, we hypothesize that intravenous CYC could have the same efficacy as oral CYC with possibly less toxicity. Given the side effects of the current standard therapy of ABMA disease, further research to refine treatments is needed.

Worsening and/or Relapse After Treatment Onset

Although ABMA disease is usually considered as a monophasic illness, relapses occur in 3%–10% of cases[11,15,16,19,20,23,28,29,35,36,42,43,49,57]. Relapses have been linked to various factors, such as reappearance or rising titers of circulating ABMA[28,35,36,42], monoclonal production of ABMA[11,23], tapering of corticosteroids and/or immunosuppressive treatment[26,35,49], coexisting ANCA vasculitis[20,29], smoking[20,21,42], hydrocarbon exposure[33], and infection[57]. No such factor was detected in our cohort, besides re-exposure to water vapor in a professional cook. Although 50% of our patients continued to smoke after AH, no significant relationship could be found between persistent active smoking and pulmonary or renal worsening after treatment onset.

Relapses have been reported to occur a few days[35] to more than a decade[19,42,49] after the initial episode. This broad range of delays makes it difficult to clearly separate a worsening in the frame of the initial episode from a relapse occurring after complete cure. We used the term ''worsening'' to describe any deterioration presenting as either a discrete event or a continuous process, and occurring at a time when improvement was expected, that is, from the day of onset of treatment. Pulmonary worsening occurred in one-third of our patients. Apart from a tendency for better initial renal function ($p = 0.04$), this subgroup could not be separated from the other patients. However, pulmonary worsening did not affect outcome. Renal worsening occurred in one-third of patients. No predictor of renal worsening could be identified, but three-quarters of these patients required dialysis and progressed to renal death. These data show that, despite appropriate therapy, deterioration of renal function cannot be prevented in a substantial proportion of patients. Importantly, pulmonary worsening did not adversely affect long-term outcome, whereas renal worsening usually led to renal death.

Pulmonary Outcome

To our knowledge the long-term pulmonary outcome in ABMA disease has been previously examined in only 1 series of 14 cases, 8 of which had initial clinical or radiologic evidence of AH[18]. Compared with a control group, the only observed change in ABMA disease was reduced TLCO/VA (46% ± 10% vs. 69% ± 15%; $p = 0.006$)[18], whereas lung volumes, exercise oxygen saturation, and maximal oxygen consumption remained similar[18]. TLCO/VA was also lower in 8 patients with AH compared with 6 patients without AH, a finding attributed to possible pulmonary fibrosis secondary to prolonged or recurrent AH[18], although this hypothesis was not supported by lung volume and exercise measurements, and pulmonary imaging was not available. Our data provide further insight into the long-term pulmonary outcome after AH in ABMA disease. Lung function measured remote from the acute phase (median delay, 11 mo) showed a moderate lung volume reduction in only 20% of cases, and normal median values. An elevated RV/TLC ratio was present in 30% at follow-up, compared with 55% during the acute phase. Although smoking may be a contributing factor to air trapping, a median smoking history of only 10 pack-years suggests that other mechanisms could be involved. Chronic airflow obstruction has been occasionally reported in AH associated with microscopic polyangiitis[58]. In agreement with previous data[18], TLCO and TLCO/VA were moderately reduced, but in only one-third of cases. Hypoxemia was no longer observed, and only a mild elevation of AaPO2 between 20 and 25 mm Hg was present in one-third of cases. Finally, last chest X-ray was normal in all patients, without any sign of pulmonary fibrosis. Thus our data show that AH in ABMA disease does not lead to significant long-term pulmonary morbidity if the patient survives the acute phase.

Renal Outcome

Several studies have shown that initial creatinine level is a strong predictor of final renal outcome, irrespective of treatment modalities[13,27,31,43,45,50,56]. In agreement with these data, our patients who evolved to renal death had significantly higher initial creatinine (median, 486 vs. 87 μmol/L; $p = 0.0002$) and higher need for dialysis (100% vs. 7%; $p = 0.0002$). Furthermore, as previously suggested by isolated cases[8,71], the current study confirms that ABMA disease with normal initial creatinine is associated with an excellent long-term prognosis, with independent renal function in 100% of cases compared with 17% in those presenting with renal insufficiency.

Survival

The survival rate was 100% in our cohort, in agreement with large recent series[12,20,27,43,50,67] where it ranged from 68%[12] to 100%[20]. Reported causes of death in ABMA disease include uncontrolled AH[27,43], cardiac arrest, infection, and gastrointestinal bleeding[12,50]. Fatal AH occurred in 7%–10% of cases[27,43].

ABMA Disease With Predominant Pulmonary Involvement

ABMA disease presenting with predominant pulmonary involvement and normal creatinine has been previously reported in isolated cases[2,8,17,39,47,51,52,63,71], or as a small minority in larger series[27,50]. The current study allows a more detailed description of this particular cohort. Most

cases had hematuria and/or proteinuria, but some had completely normal urinary sediment, as occasionally reported[8,47]. These data emphasize the need to search systematically for ABMA disease in patients presenting with AH and only minor, or even absent, clinical renal involvement. Furthermore, the absence of circulating ABMA is not sufficient to rule out ABMA disease, which may be demonstrated at renal biopsy. Although the decision to perform a renal biopsy may be difficult in the absence of detectable renal disease, this procedure may definitely establish or rule out the diagnosis of ABMA disease at an early stage, with a significant impact on prognosis. It remains unclear whether this subset of ABMA disease with predominant pulmonary involvement represents just an early disease stage, or a true variant of disease expression. In support of the former, we observed a worsening of renal parameters between hospital admission and treatment onset in 4 of 10 evaluable patients. We therefore consider that AH with predominant pulmonary involvement may evolve to the full-blown pulmonary-renal ABMA disease, thus justifying rapid diagnosis and treatment. Hence, AH may precede urine abnormalities or glomerulonephritis by weeks, and even years[7]. Since initial renal function is a major determinant of renal outcome, early diagnosis before onset of renal insufficiency is likely to have a major impact on renal prognosis. Our data also show that patients exposed to an inhaled agent (other than tobacco smoke) had significantly better initial renal function, suggesting that this exposure triggered AH at an early disease stage. Detecting such an exposure at presentation may thus also contribute to an earlier diagnosis and better outcome.

In summary, the current series of patients with strictly defined AH recruited by pulmonary physicians differs in several aspects from previous series recruited by nephrology groups, and thus brings specific information on the pulmonary manifestations of ABMA disease. We conclude that 1) BAL is more sensitive than hemoptysis, hypoxemia, anemia, or pulmonary opacities to detect AH, and may be considered the gold standard of AH diagnosis; 2) active smoking and exposure to various inhaled agents are highly prevalent in this population, suggesting a pathogenic or triggering role; 3) ABMA disease should be considered in patients presenting with AH after inhalation of cocaine or other agents; 4) subclinical AH may occur in ABMA disease, and may persist after apparently complete clinical cure; 5) initial renal function is the strongest determinant of long-term renal outcome and thus, in patients with predominant pulmonary involvement, early detection of AH by BAL may allow appropriate treatment before appearance of renal insufficiency and thus improve renal outcome; 6) the absence of circulating ABMA is insufficient to rule out ABMA disease, and renal biopsy may be diagnostic, even if renal function and urinary sediment are normal; 7) long-term pulmonary outcome is characterized by mild TLCO/VA reduction and AaPO2 elevation without respiratory insufficiency, in sharp contrast with renal outcome; 8) hemoptysis, hypoxemia, or chest opacities may recur in one-third of patients after treatment onset, but do not affect long-term pulmonary outcome; 9) worsening of renal function occurs despite treatment in one-third of cases and adversely affects renal outcome; and 10) long-term renal outcome is excellent in patients with predominantly pulmonary involvement and normal initial serum creatinine.

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