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MICROSCOPIC POLYANGIITIS

Clinical and Laboratory Findings in Eighty-Five Patients

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Objective. **To retrospectively analyze the clinical symptoms, laboratory findings, and outcomes in patients with microscopic polyangiitis (MPA) who were enrolled in various clinical trials conducted by the French Vasculitis Study Group.**

Methods. **A cohort of 85 patients meeting the Chapel Hill criteria for MPA participated in the study. Seventy-one of them were included in prospective therapeutic trials. Eighty-one diagnoses were biopsy proven. In the other patients, diagnosis was based on clinical findings.**

Results. **Forty-seven men and 38 women, with a mean ± SD age of 56.8 ± 14.6 years, met the criteria for MPA. Their main clinical symptoms were renal manifestations (78.8%), weight loss (72.9%), skin involvement (62.4%), fever (55.3%), mononeuritis multiplex (57.6%), arthralgias (50.6%), myalgias (48.2%), hypertension (34.1%), lung involvement (24.7%; alveolar hemorrhage 11.8%), and cardiac failure (17.6%). The mean ± SD serum creatinine level before treatment was 2.59 ± 2.96 mg/dl; 47 patients had renal insufficiency (serum creatinine >1.36 mg/dl). Eight patients underwent dialysis at the time of diagnosis, and long-term dialysis was necessary for 10 patients. Antineutrophil cytoplasmic antibodies (ANCA) were present in 38 of 51 patients (74.5%), of whom 33 had a perinuclear staining pattern (pANCA) and 5 had a cytoplasmic pattern. Antibodies to proteinase 3 were present in 4 patients and antibodies to myeloperoxidase were detected in 31, as determined by enzyme-linked immunosorbent assay. Of the 30 patients who underwent renal and celiac angiography, 4 had microaneurysms. Of the 29 patients (34.1%) who had relapses, 8 died during or after the relapse. During followup, 28 of the 85 patients (32.9%) died. The mean ± SD duration of followup of the group was 69.9 ± 60.6 months. Deaths were less frequent when patients had been treated with steroids and immunosuppressive drugs (13 patients [24.1%]) than with steroids alone (15 patients [48.4%]) ($P < 0.01$). The 5-year survival rate was 74%.**

Conclusion. **This study demonstrated that MPA is a multisystemic disease in which renal symptoms are frequent, but the disease is also associated with general symptoms, arthritis, mononeuritis multiplex, and other manifestations that are also seen in various vasculitides. The rarity of abnormal angiogram findings and the high frequency of pANCA are characteristic of MPA. In most cases, the outcome is comparable with those of other systemic vasculitides, but relapses are frequent.**

Microscopic polyangiitis (MPA) is a systemic vasculitis that is histologically characterized by small-vessel involvement. MPA was initially recognized as a particular type of polyarteritis nodosa (PAN) with, in most cases, rapidly progressive necrotizing glomerulonephritis (RPGN) and sometimes with lung hemorrhage (1). A group of experts held an international consensus conference and attempted to distinguish MPA from classic PAN (2). The proposed feature distinguishing PAN from MPA (formerly, microscopic polyarteritis) is

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the absence (versus the presence) of vasculitis in the arterioles, venules, or capillaries. Small-vessel involvement, when present, is the definitive diagnostic criterion of MPA and excludes the diagnosis of PAN, even if medium-sized arterial lesions are seen. This classification minimizes the frequency of a classic PAN diagnosis because small-vessel involvement excludes it (3).

The purpose of this retrospective study was to analyze the clinical and biologic manifestations, outcomes, and treatments in a cohort of patients who were diagnosed with MPA according to the Chapel Hill consensus criteria (2).

PATIENTS AND METHODS

Patient selection. Patients were selected from the database of the French Vasculitis Study Group, which was developed over the last 15 years from several multicenter therapeutic trials on PAN, Churg-Strauss syndrome (4–8), and Wegener's granulomatosis (9). Clinical and laboratory data had been collected prospectively. The Cooperative Study Group for Polyarteritis Nodosa, a subgroup of the French Vasculitis Study Group, participated in this study; its members are listed in Appendix A.

Inclusion criteria for MPA were the following signs and symptoms, in variable combinations: 1) presence of RPGN and/or alveolar hemorrhage, which could be associated with other systemic manifestations of vasculitis; 2) histologic demonstration of small-sized vessel vasculitis or segmental pauci-immune necrotizing glomerulonephritis (GN); or 3) symptoms suggesting small-vessel involvement, e.g., purpura, without GN and/or alveolar hemorrhage. Patients with isolated small-vessel vasculitis were not included, and only systemic vasculitis was considered. Although we have previously established that antineutrophil cytoplasmic antibody (ANCA)–positive patients should be considered to have MPA (10), ANCA were not included as a criterion in this analysis, because we used only the Chapel Hill criteria. We did, however, attempt to determine the frequency of ANCA in the MPA patients.

Patients with other small-vessel angiitides, such as Wegener's granulomatosis, malignancy-associated vasculitis, or connective tissue disease–associated vasculitis, were excluded from the study. The presence of cryoglobulinemia was exclusionary, as was the presence of IgA deposits in skin biopsy specimens or other biopsy samples, since this could be indicative of Henoch-Schönlein purpura. When ear, nose, and throat involvement or lung nodules were present, patients were not included in the study. Although it is not easy to differentiate between Wegener's granulomatosis and MPA, the long duration of followup enabled the diagnosis of MPA to be confirmed. Most biopsy samples were reviewed by 2 pathologists (PC for the renal samples and JA for the others).

Laboratory tests. ANCA have been systematically investigated since the late 1980s. The retrospective ANCA tests were all performed at the French reference center by L. H. Noël and Ph. Lesavre (Hôpital Necker, Paris, France) and members of the European Standardization Workshop (11). ANCA positivity was assessed in only 51 of the 85 patients included in this study.

Samples of patients' sera (of which 7 were frozen samples that had been stored in our center) were tested for the presence of ANCA using an indirect immunofluorescence assay. Neutrophils from healthy individuals were isolated by density-gradient centrifugation, and then contaminating red cells were eliminated by hypotonic lysis. Cytocentrifuged preparations were made, and each slide was fixed for 5 minutes in 100% ethanol, dried, incubated with serum (diluted 1:10 and 1:20) for 30 minutes at 4°C, and then washed with phosphate buffered saline. Cells were labeled with a fluorescein isothiocyanate–conjugated anti-immunoglobulin ($F[ab']_2$ anti-IgG, IgA, or IgM), washed, and examined using a fluorescence microscope. ANCA were also detected using an enzyme-linked immunosorbent assay (ELISA) according to the recommendations of the European Standardization Workshop (11). Although ANCA were assayed in different laboratories, the detection technique was consistent with the recommendations detailed above.

Serologic evaluations were performed to test for hepatitis B virus (HBV) in all 85 patients, human immunodeficiency virus (HIV) infection in 84 of 85 patients, and hepatitis C virus (HCV) in 45 of 85 patients. ANCA, serum creatinine, proteinuria, hematuria, and leukocyturia were measured at the time of diagnosis and then serially throughout the study.

Treatment. Seventy-one patients were enrolled in prospective therapeutic trials organized by the French Vasculitis Study Group; the results have been published elsewhere (4–9). These 71 patients received the treatments being administered in the trials at the time of inclusion. Randomization to treatment groups was centralized in the coordinating center (Hôpital Avicenne) and had been done by phone or fax. Selection for the present study was confirmed after a careful check of inclusion and exclusion criteria. The other 14 patients were treated with steroids and cytotoxic drugs independent of their disease severity. Plasma exchange (PE) was not prescribed initially to this group of patients. The common guidelines for treatment are detailed below.

Steroids. Corticosteroids (CS) were prescribed to every patient. For 68 patients who were included in the prospective trials, therapy was initiated with intravenous (IV) pulse methylprednisolone at a dosage of 15 mg/kg/day for 3 consecutive days. Then, oral prednisone was given at an initial dosage of 1 mg/kg/day for 1–2 months. As a function of the clinical response and the evolution of laboratory parameters, the dosage of prednisone was tapered and stopped according to the schedule reported elsewhere (4,9).

Cyclophosphamide. Thirty-nine patients received either monthly IV pulses of cyclophosphamide (CYC) at a dosage of 0.6 gm/m^2 for 6 months (5 patients) or 1 year (25 patients) or oral CYC at a dosage of 2 mg/kg/day for 1 year (9 patients). For patients who were assigned pulse therapy, the first IV pulse of CYC was administered on day 4 after the 3 IV pulses of methylprednisolone. Patients' white blood cell counts were monitored (10–14 days after the IV pulse and 2 days preceding the next one), so that the CYC dosage could be adjusted to avoid severe neutropenia (defined as a neutrophil count $<$1,500 cells/mm^3). In the case of renal insufficiency or for patients $>$65 years old, the dose was 0.5 gm/m^2 until normal renal function was restored. Hydration and adjunctive treat-

ment with mesna (Uromitexan) were systematically included in this regimen. The oral dose was adapted to white blood cell counts as explained above. Treatment was stopped after 1 year, except in the case of treatment failure or relapses. Since 1991, after the description of *Pneumocystis carinii* pneumonia in Wegener's granulomatosis patients treated with CS and CYC (12), it was strongly recommended that CD4 lymphocyte counts be monitored. In the case of a CD4+ cell count of $<300/mm^3$, cotrimoxazole prophylaxis against *Pneumocytis carinii* pneumonia (one 400-mg tablet/day of trimethoprim/sulfamethoxazole) was prescribed.

Plasma exchanges. Thirty-seven patients also underwent PE, of whom 24 were participating in the protocols comparing CS plus PE therapy with CS plus PE plus oral CYC (4) or CS with CS plus PE (5). In every protocol that included PE, patients received 3 PE per week for 3 weeks and then, depending on the protocol, the dosage was tapered to a monthly administration for 6 months (4), progressively tapered over 2 months (5), or abruptly stopped after 3 weeks (9). The amount of plasma scheduled to be exchanged during each session was 60 ml/kg of body weight. The replacement fluid consisted of 500 ml of fluid gelatin and 4% albumin. Fresh-frozen plasma was used in some situations, mainly for patients with decreased levels of coagulation factors. When side effects from PE occurred or when venous access was not possible, PE were temporarily stopped or withdrawn.

Miscellaneous. One HBV-positive patient received one course of vidarabine in conjunction with PE; however, she did not respond to treatment. After careful reexamination of her chart, a diagnosis of MPA was made and HBV infection was considered coincidental. The patient was then successfully treated with CS. One patient received CS in combination with 1 year of azathioprine.

Followup. Followup was comparable for all patients, comprising, once remission was obtained, 2 visits to their referring physicians each year for 5 years, then 1 visit per year for the subsequent years. When patients were considered to be in complete remission or recovered, visits to the referring center were no longer required and any further information concerning the patient was transmitted by the general practitioner or specialist in charge to the coordinating center. Clinical remission was recorded when there was a stabilization or attenuation of clinical symptoms and normalization of laboratory abnormalities (except ANCA). Relapses were defined as new systemic manifestations of vasculitis or worsening of 1 or several of the initial manifestations of the disease.

Evaluation of disease activity and prognostic factors. To predict the outcome in patients, we used the five-factor score (FFS) (13), which comprises the following items: classes of serum creatinine (<1.58 and >1.58 mg/dl) and proteinuria (>1 gm/day), and the presence of severe gastrointestinal (GI) tract involvement, cardiomyopathy, and central nervous system (CNS) involvement. The presence of each factor was accorded 1 point. Three classes of scores were defined: 0, when no factor was noted; 1, when 1 factor was present; and 2, when 2 or more factors were present. We have previously demonstrated (13) that the FFS is significantly correlated with mortality.

We also applied the Birmingham Vasculitis Activity Score (BVAS) (14) at the time of diagnosis, to test its ability to correlate with the initial disease prognosis and to compare it with that of the FFS. The BVAS is a clinical index of disease activity that is based on symptoms and signs in 9 separate organ systems. Disease features are only considered when they are attributable to active vasculitis. For the BVAS, the threshold of 23 points, the average patient score at the time of diagnosis, was arbitrarily chosen to define 2 categories of patients (those with a BVAS ≤ 23 and those with a BVAS >23) for whom prognosis and outcome were evaluated.

Statistical analysis. For univariate analysis, tests were carried out using the usual parametric methods, i.e., chi-square test with Yates' correction for small numbers, when appropriate, for comparison of qualitative variables, and Student's *t*-test for comparison of quantitative variables. Values were expressed as the mean ± SD. Mortality rates and odds ratios were calculated for every item that could be a predictor of death. The variables tested were age, sex, weight loss $>10\%$ of body weight, myalgias, arthritis, mononeuritis multiplex, skin manifestations, GN, proteinuria <1 gm/day and >1 gm/day, renal insufficiency (serum creatinine >1.36 mg/dl), severe GI tract symptoms (i.e., bleeding, bowel perforation, pancreatitis), cardiomyopathy, CNS symptoms, pulmonary manifestations, and an erythrocyte sedimentation rate (ESR) <30 mm/hour and >30 mm/hour. Multivariate analysis of the predictive power of baseline variables for mortality used a stepwise logistic regression model for the entire population. It focused only on items that were significantly associated with increased mortality according to the univariate analysis. The FFS and BVAS were also subjected to multivariate analysis and a correlation was established between the 2 scores. Several treatments were also subjected to univariate and multivariate analyses: CS as a single treatment, CS combined with cytotoxic drugs, and PE regardless of the adjunctive treatments.

Statistical calculations were made using the Statview statistical package (Abacus Concepts, Berkeley, CA). Survival as a function of major predictive factors and of prognostic scores was analyzed according to the Kaplan-Meier method (15) using the log-rank statistical test (16). The SPSS statistical package (SPSS, Chicago, IL) was used.

RESULTS

Eighty-five patients with MPA (47 men and 38 women, mean age 56.8 ± 14.6 years, range 16–86 years) were followed up between 1969 and 1995. Eighty-two of them were Caucasians of European origin, and 1 each was from northern Africa, Madagascar, and China. None of the patients had a history of systemic disease or allergy. The patients' general condition was poor at the beginning of the disease, with fever (n = 47) and anorexia or weight loss (n = 62). Eighty-one diagnoses of MPA were biopsy proven. For the other patients, diagnosis was based on clinical signs. The mean ± SD weight loss before diagnosis was 5.3 ± 4.7 kg, and the reduction in weight began 2 ± 2.1 months before diagnosis.

Among the clinical manifestations detailed in

Table 1. Clinical manifestations observed in the entire study population (n = 85)*

Mean ± SD age (range), years	56.8 ± 14.6 (16–86)
Sex ratio, M:F	47:38
Renal manifestations†	67 (78.8)
Weight loss	62 (72.9)
Skin involvement	53 (62.4)
Purpura	35 (41.2)
Livedo	11 (12.9)
Nodules	11 (12.9)
Urticaria	3 (3.5)
Fever	47 (55.3)
Mononeuritis multiplex	49 (57.6)
Superficial peroneal nerve	43 (50.6)
Deep peroneal nerve	23 (27.1)
Cubital	18 (21.2)
Radial	10 (11.8)
Bilateral	47/49 (95.9)
Unilateral	2/49 (4.1)
Cranial nerve involvement	6 (7.1)
Arthralgias	43 (50.6)
Myalgias	41 (48.2)
Vascular manifestations	43 (50.6)
Hypertension	29 (34.1)
Cardiac failure	15 (17.6)
Pericarditis	9 (10.6)
Digital ischemia	6 (7.1)
Myocardial infarction	2 (2.4)
Gastrointestinal tract involvement	26 (30.6)
Lung involvement	21 (24.7)
Alveolar hemorrhage	10 (11.8)
Pneumonitis	9 (10.6)
Pleuritis	5 (5.9)
Eye involvement	1 (1.2)
Central nervous system involvement	10 (11.8)
Orchitis	1/47 (2.1)
Sinusitis	1 (1.2)

* Except where otherwise indicated, values are the number (%).
† Detailed in Table 2.

Table 1, fever, weight loss, renal manifestations, and mononeuritis multiplex were the most frequent. Ten patients experienced alveolar hemorrhage, and in 8 of the 10 patients, this sign was part of a pulmonary-renal syndrome that included acute renal insufficiency, hemoptysis, dyspnea, anemia, and alveolar shadowing on the chest radiograph. In 7 of the 10 patients, alveolar hemorrhage was associated with purpura, and in 6, with arthromyalgias and fever. In 2 of the 10 patients, hemoptysis preceded the other manifestations of vasculitis by several weeks or months. For 1 of them, vasculitis was misdiagnosed and the patient received a full course of antituberculosis treatment before the onset of renal insufficiency and the other symptoms of vasculitis. Hypertension was noted in 29 patients. Orchitis was found in 1 patient.

Renal signs were present in 67 patients (78.8%) (Table 2). The mean ± SD serum creatinine level was 2.59 ± 2.96 mg/dl (range 0.58–17 mg/dl) at presentation, and 8 patients urgently required dialysis. Proteinuria (range 0.5–6 gm/day) was present in 54 patients, hematuria was detected simultaneously in 45, and leukocyturia was noted in 30.

GI manifestations comprised abdominal pain in 23 patients, melena in 4, hematemesis in 3, bowel perforation in 1, cholecystitis in 2, appendicitis in 1, and pancreatitis in 1. An ESR >30 mm hour was measured in 79 patients (92.9%), and their mean ESR was 84.8 ± 33.9 mm/hour. Liver function tests yielded normal findings in 75 patients (88.2%); in the other 10 patients, the aspartate aminotransferase and/or alanine aminotransferase levels were twice the normal range. The hepatitis B e antigen was found in 2 patients, anti-HCV antibodies in 1, and HIV in none. When HBV or HCV infection was present, there was no clinical evidence that the viral infection was responsible for the vasculitis, and the infection was therefore considered to be coincidental. Cryoglobulinemia was not found and complement levels were normal. Patients with elevated transaminase levels had no detectable viral antigens, antibodies to virus, or molecular biologic evidence of virus replication. Among the autoantibodies tested, rheumatoid factor was found in 14 of 61 patients (23%) and antinuclear antibodies in 12 of 71 (16.9%). No evidence for vasculitis associated with connective tissue disease was ever found.

At the time of diagnosis, ANCA were present in 38 of 51 patients (74.5%), of whom 33 had a perinuclear staining pattern (pANCA) and 5 had a cytoplasmic pattern (cANCA). Antimyeloperoxidase (anti-MPO) antibodies were detected by ELISA in 31 patients and anti–proteinase 3 (anti-PR3) antibodies in 4. Specificity data were not available for all patients. Among the patients with GN, ANCA were detected in 15 of the 25 patients tested for these antibodies (60%). Six of the 8 patients with alveolar hemorrhage who were tested for

Table 2. Detailed distribution of the renal manifestations observed in 67 patients with microscopic polyangiitis (MPA)*

Mean ± SD serum creatinine level, mg/dl	2.54 ± 2.96
Renal insufficiency*	47 (70.1)
Dialysis at onset of MPA	8 (11.9)
Secondary dialysis	6 (9)
Glomerular syndrome	55 (82.1)
Nephrotic syndrome	10 (14.9)
Proteinuria	54 (80.6)
Hematuria	45 (67.2)
Leukocyturia	30 (44.8)

* Except where otherwise indicated, values are the no. (%).
† Defined as serum creatinine value >1.36 mg/dl.

Table 3. Cause of death and time until death in 28 patients during the study period*

Cause of death	Number of deaths	Time until death, months
Systemic vasculitis		
RPGN	1	1
Pancreatitis	1	0.5
CNS vasculitis	1	1
Alveolar hemorrhage	2	3, 99
Ruptured aneurysm	1	6
Uncontrolled vasculitis	2	19, 105
Cardiac failure	1	22
Myocardial infarction	1	100
Infection		
Pneumocystis carinii pneumonia	1	99
Septicemia	6	3, 4, 4.5, 49, 51, 104
Mucormycosis	1	8
Other cause		
Respiratory failure	1	7
Bedridden†	1	53
Liver cirrhosis	1	156
Lymphoma	1	76
Metastatic cancer	2	25, 55
Hepatic coma	1	64
Cardiac failure	1	136
Coronary heart disease	1	58
Pulmonary embolism	1	4

* RPGN = rapidly progressive necrotizing glomerulonephritis; CNS = central nervous system.
† Extremely poor general condition.

ANCA were positive. Of the 30 patients who underwent abdominal and renal angiography, 4 had microaneurysms and/or stenoses. Three of these patients also had GN. The fourth had only 1 microaneurysm of a brain artery, which was not considered to be due to vasculitis.

Histologic samples were obtained from 81 patients, some of whom had more than 1 diagnostic biopsy. The diagnosis in 51 patients was based on skin, muscle, or nerve biopsy. Renal biopsy samples obtained from 36 patients showed pauci-immune GN in 35 and tubulointerstitial nephritis associated with moderate glomerular changes in 1. Ten liver biopsies were also performed, of which 3 showed vasculitis. In 5 patients, vasculitis was diagnosed based on histologic examination of surgically removed specimens (2 small intestine, 2 appendices, 1 gallbladder).

The mean ± SD duration of followup was 69.9 ± 60.6 months. During the course of the trials, 28 of the 85 patients (32.9%) died of various causes, as detailed in Table 3. Eight patients started dialysis at the time of diagnosis, but during treatment, it was possible to stop dialysis in 4. Two of these 4 patients died, 1 from alveolar hemorrhage and the other from lymphoma. The 4 patients who remained on dialysis are alive. In addition, 6 patients suffered a relapse with the development of renal insufficiency that required dialysis; 2 of them died during the relapse. At the end of the study, 10 patients were undergoing long-term dialysis.

Twenty-nine patients (34.1%) relapsed after a mean ± SD time of 42.9 ± 40.4 months (range 5–144 months). Five of them suffered a second relapse, 1 patient experienced 3 relapses, and 1 had >3 relapses. Eight patients died, of whom 6 died during or after the first relapse, none during a second relapse, and 2 after ≥2 relapses. Relapse symptoms and their severity are summarized in Tables 4 and 5.

The mean age of patients who died was higher, but not significantly different, than that of survivors (62 versus 55 years). Twenty patients experienced a relapse that reproduced one of the initial symptoms of MPA, and 9 had new symptoms. In 18 patients, the relapse was mild and/or comparable with or less severe than the initial presentation of the disease, but in 11, relapse manifestations were more acute and potentially more severe. Among the patients who experienced a relapse, 17 had been tested for ANCA, of whom 15 (88.2%) were ANCA positive at the time of disease onset and 10 at the time of relapse.

We also attempted to evaluate the influence of treatment on the relapse rate and mortality. Due to the diversity of the trials conducted, patients were classified according to major therapeutic regimens: one group of 54 patients received CS and cytotoxic agents (CYC for 52 patients and azathioprine for 2) and the other group of 31 patients was treated initially with CS alone. In the former group, 13 (24.1%) died, compared with 15 (48.4%) in the latter group receiving CS alone ($P < 0.01$). Seventeen relapses occurred (31.5%) in the former group treated with immunosuppressors, versus 12 (38.7%) in the latter group (P not significant [NS]). With regard to the influence of PE, which was given to 37 patients, 12 patients (32.4%) in the group receiving PE relapsed compared with 17 (35.4%) in the group without PE (P NS). Fourteen patients (37.8%) who were treated with PE died, versus 14 (29.2%) in the group without (P NS).

Prognostic factors and scores. The mean FFS was 1.8 (±1.3 SD) and the mean BVAS was 23.7 (±8 SD). According to univariate analysis, the only factors significantly associated with increased mortality were proteinuria >1 gm/day ($P < 0.007$) and renal insufficiency (serum creatinine >1.36 mg/dl) ($P < 0.002$). According to multivariate analysis, proteinuria was the only factor significantly associated with increased mortality ($P < 0.01$). Comparison of the FFS and BVAS by

Table 4. Initial microscopic polyangiitis manifestations among patients who had a relapse*

Patient	Main initial manifestations
1	Arthralgias, pleuritis, myocarditis, GN, cranial nerve palsy
2	Fever, weight loss, myalgias, purpura
3	Fever, myalgias, purpura, cardiomyopathy, renal insufficiency, GN, abdominal pain
4	Purpura, episcleritis, myocarditis, GN, mononeuritis multiplex, CNS involvement
5	Fever, myalgias, cardiomyopathy, renal insufficiency, GN
6	Fever, weight loss, arthralgias, alveolar hemorrhage, GN, mononeuritis multiplex
7	Fever, weight loss, myalgias, abdominal pain, GN, renal insufficiency, mononeuritis multiplex
8	Fever, weight loss, purpura, myalgia, renal insufficiency, mononeuritis multiplex
9	Fever, weight loss, myalgias, skin nodules, abdominal pain, GN
10	Fever, weight loss, myalgias, arthralgias, purpura, alveolar hemorrhage, melena, mononeuritis multiplex
11	Fever, weight loss, purpura, GN, mononeuritis multiplex
12	Weight loss, fever, alveolar hemorrhage, GN
13	Arthralgias, myalgias, cranial nerve palsy
14	Fever, weight loss, purpura, alveolar hemorrhage, renal insufficiency
15	Fever, weight loss, myalgias, arthralgias, gangrene, skin nodules, GN, mononeuritis multiplex
16	Fever, weight loss, myalgias, GN
17	Weight loss, purpura, myocarditis, renal insufficiency, GN, mononeuritis multiplex
18	Purpura, bowel vasculitis
19	Weight loss, mononeuritis multiplex, alveolar hemorrhage
20	Weight loss, fever, arthritis, cholecystitis, renal insufficiency
21	Fever, livedo, weight loss
22	Fever, weight loss, cardiac failure, GN, renal insufficiency, neuropathy
23	Fever, weight loss, purpura, alveolar hemorrhage, abdominal pain, renal insufficiency, GN
24	Weight loss, myalgias, arthralgias, renal insufficiency, GN, mononeuritis multiplex
25	Arthralgias, abdominal pain, mononeuritis multiplex
26	Myalgias, arthralgias, skin nodules
27	Skin nodules, abdominal pain, mononeuritis multiplex
28	Weight loss, pleuritis, cardiomyopathy, renal insufficiency, GN, mononeuritis multiplex
29	Purpura, mononeuritis multiplex, renal insufficiency, tubulointerstitial nephritis, moderate glomerular changes

* GN = glomerulonephritis; CNS = central nervous system.

multivariate analysis showed that only the FFS significantly predicted an increased risk of mortality ($P < 0.01$). Multivariate analysis also showed that cytotoxic drugs were significantly associated with lower mortality ($P < 0.01$). The regression coefficient for the BVAS versus death was 0.196 ($P < 0.08$) and that for the FFS versus death was 0.256 ($P < 0.02$). Comparison of the FFS and BVAS showed that they were significantly correlated ($r = 0.539$, $P = 0.0001$).

Clinical signs, biologic parameters, and scores were also tested as predictors of remission. The serum creatinine level was the only biologic sign that could predict remission ($P < 0.05$). We observed that a significantly higher number of patients with an FFS of 1 (23.7%) or an FFS of 2 (68.4%) than those with an FFS of 0 (7.9%) received PE ($P < 0.05$), in accordance with

Table 5. Microscopic polyangiitis manifestations signaling relapse*

Patient	Relapse manifestations	Time until first relapse (months)	Number of relapses
1	Cardiac insufficiency	25	1
2	Myalgias	43	2
3	Ruptured hepatic aneurysm leading to death	6	1
4	Arthritis, inflammatory syndrome	89	2
5	Cardiac insufficiency leading to death	22	1
6	Alveolar hemorrhage leading to death	99	1
7	GN relapse, more severe	121	1
8	Mononeuritis relapse, less severe	31	1
9	Skin nodules, disseminated vasculitis leading to death	18	1
10	Purpura	27	2
11	Arthralgias, episcleritis	53	1
12	Poor condition, inflammatory syndrome	31	1
13	Arthralgias, myalgias, inflammatory syndrome leading to death	100	3
14	Purpura, less severe	41	1
15	Arthralgias, myalgias	94	1
16	Sensory neuropathy	54	1
17	Infection in uncontrolled disease leading to death	48	1
18	Bowel vasculitis, comparable to initial manifestations	60	1
19	Arthralgias	19	1
20	Asthenia, sensory neuropathy	60	1
21	Skin nodules	59	1
22	Abdominal pain, weight loss, inflammatory syndrome	78	1
23	Asthenia, sensory neuropathy	116	1
24	Multiorgan failure, septicemia leading to death	104	1
25	Skin nodules, weight loss, myalgias	123	2
26	Skin vasculitis, arthralgias	13	1
27	Skin nodules, myalgias, ischemic colitis	281	2
28	Renal insufficiency, more severe, inflammatory syndrome leading to death	120	>3
29	Purpura, fever	14	1

* GN = glomerulonephritis.

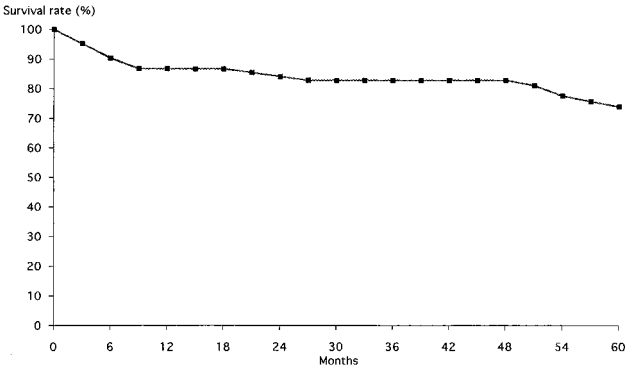

Figure 1. Five-year survival rate for the 85 patients with microscopic polyangiitis.

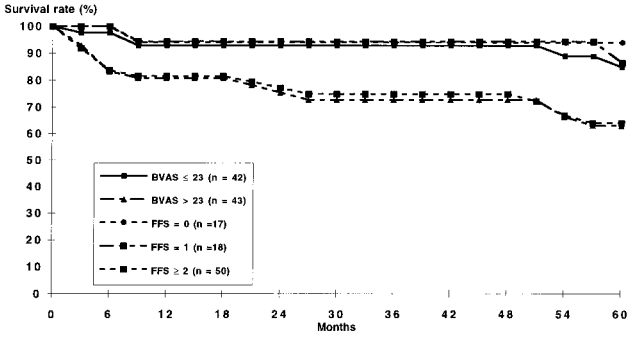

Figure 3. Survival rates for the 85 patients as a function of the five-factor score (FFS) and the Birmingham Vasculitis Activity Score (BVAS).

the inclusion criteria in prospective trials. Unlike the FFS, the BVAS was not able to detect any difference in the disease severity of patients with or without PE (mean BVAS 25.2 in the group with PE versus 22.4 in the group without; *P* NS). The 5-year survival rate was 74%. Survival curves for the 85 patients and survival as a function of proteinuria and of the FFS and the BVAS are shown in Figures 1, 2, and 3, respectively.

DISCUSSION

Among the group of diseases formerly called PAN, an entity designated MPA was first described by Wohlwill (17), and its characteristics were subsequently clearly established by Davson et al (1), who suggested that the segmental necrotizing GN observed in PAN was linked to a microscopic form of the disease that was distinct from the PAN described by Küssmaul and Maier (18). MPA is characterized histologically by the involvement of small vessels (i.e., capillaries, venules, or arterioles) and the absence of granuloma. Microscopic PAN is now considered to be synonymous with MPA. However, regardless of the designation used, RPGN is one of its major characteristics. Other clinical symptoms that occur during MPA, such as alveolar hemorrhage, constitute a pulmonary-renal syndrome similar to that also observed in Goodpasture's syndrome or Wegener's granulomatosis.

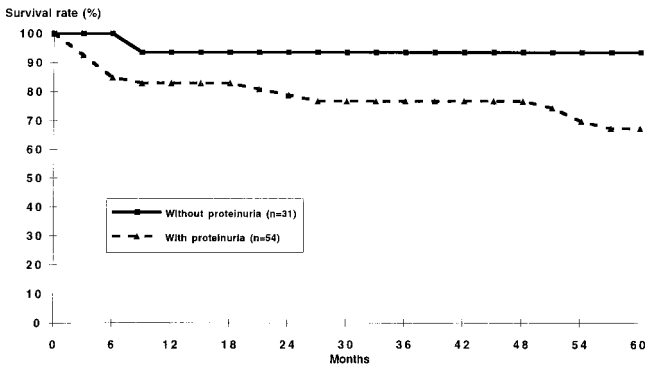

Figure 2. Survival rates for the 85 patients according to the presence or absence of proteinuria.

In this study, patients were selected based on the diagnostic criteria defined by the Chapel Hill consensus conference (2), which are not limited to the presence of RPGN or alveolar hemorrhage. The definition of MPA established in the Chapel Hill consensus nomenclature (2) is based on the presence of small-vessel involvement and not on clinical criteria. Herein, we attempted to determine which clinical characteristics and laboratory test values might be able to distinguish between MPA and PAN.

MPA, unlike PAN, cannot always be considered to be an acute disease that develops within a few weeks or days. The long time lapse between the onset of symptoms and diagnosis clearly illustrates the difficulty faced in recognizing MPA when a single organ is involved. Sometimes, after an initial indolent course, an acute episode induces the patient to consult a physician. Savage et al (19) observed that general symptoms, such as arthralgias or hemoptysis, might occur several months or years before the acute phase of the disease. MPA affects men more often than women. In the present study, the male:female sex ratio was 1.24. As has been reported by others (19,20), the average age at onset was >50 years.

The multisystemic presentation of MPA that we found is in accordance with findings in other series of

patients (19–21), although the departments from which the cases were collected were different. Our study shows that MPA can indeed be present without GN or alveolar hemorrhage, and that it is often a more general disease characterized by multivisceral involvement. Nevertheless, RPGN remains a major symptom of MPA. Indeed, it was the original reason to distinguish this entity, and previous authors have emphasized this (19–21). Although GN was present in every case diagnosed by nephrologists, it was observed in only 78.8% of our patients. The frequency of renal symptoms will probably decrease once more precise diagnostic criteria are established.

Hemoptysis may be the first symptom of severe lung hemorrhage, which is characterized by dyspnea and anemia, and may precede diffuse alveolar damage due partially or entirely to capillaritis. It was rarely observed in our patients, but this symptom might be underdiagnosed. Subclinical alveolar hemorrhage is common in patients with vasculitis who are recruited from rheumatology departments, as shown by Schnabel et al (22), who noted that 11 of 38 patients with various systemic rheumatic diseases and 29 of 56 patients with ANCA-associated vasculitides without hemoptysis had abnormal bronchoalveolar lavage findings suggesting subclinical alveolar hemorrhage. Indeed, in 2 of our patients, hemoptysis occurred 1 year before the diagnosis of MPA.

In contrast to nephrology series, systemic manifestations were more frequent and severe in our patients. For example, mononeuritis multiplex was present in 57.6% of our patients, but in only 14% of those diagnosed by nephrologists (20). GI tract involvement was as frequent as that seen in patients with PAN and Churg-Strauss syndrome. The GI involvement may be severe and in 2 patients, was responsible for death. Skin involvement was more frequent than in PAN and reflects the small-vessel involvement.

The main renal manifestation was GN. Indeed, untreated RPGN was the primary cause of renal failure and the main reason for dialysis. Renal insufficiency occurred in 70.1% of our patients, but renal function improved with treatment in most of them. Even among patients receiving dialysis, it was possible to improve renal function and, sometimes, to stop dialysis. In the long term, renal insufficiency can occur because of a new flare of the disease or scarring of glomeruli. Proteinuria and microscopic hematuria were not always present. In fact, proteinuria can be <0.50 gm/day and wrongly ignored by the clinician. The coexistence of GN and renal infarcts was proven in 2 cases, thereby demonstrating the possible overlap in features with PAN.

Among our patients, 74.5% of those tested were positive for ANCA. Jennette et al (23) demonstrated that pANCA is the staining pattern obtained with sera from ~50% of MPA patients. The antibodies were often directed against MPO. However, anti-MPO antibodies can also be detected in other systemic vasculitides and occasionally, in patients with rheumatoid arthritis, systemic lupus erythematosus, and inflammatory bowel disease. In addition, antibodies directed against PR3 may be present in MPA, but less frequently, as was the case for 4 of our patients. The PR3 detection antigen could lead to a diagnosis of Wegener's granulomatosis, but the long duration of followup of our 4 patients tended to reject this hypothesis and to confirm the diagnosis of MPA. The value of ANCA is high for MPA diagnosis, and we think that ANCA positivity should be considered diagnostic for this disease and exclusionary for classic PAN (24). ANCA may also be associated with a high relapse rate, as suggested by our observations. Nevertheless, this possibility needs to be confirmed in prospective trials.

The overall mortality rate for our 85 patients was 32.9%, which is not different from that observed for patients with PAN, Churg-Strauss syndrome, or Wegener's granulomatosis with comparable initial prognostic factors. Relapses of MPA are more frequent than those of PAN, which have been observed in 7% of cases (25), or those of Churg-Strauss syndrome, which have occurred in 23.8% of patients (Guillevin L et al: unpublished data). Some authors considered the relapses to be less severe or of equal severity as the initial manifestations of the disease (26). Although we observed that this notion held true in the majority of cases, we also documented relapses that were more severe and even responsible for death. The severity of relapses cannot be predicted. Most patients relapsed only once, but multiple relapses can occur. The number of relapses was not correlated with mortality.

The influence of treatment on mortality and relapses has to be interpreted with caution because this study was retrospective, and therapeutic regimens were heterogeneous despite some similarities. Effects of treatments have been more thoroughly analyzed in prospective studies published elsewhere (4–10). Nevertheless, we observed that PE did not prevent relapses and did not influence the mortality rate (5–8). The relapse rate was also not significantly modified by cytotoxic agents, but they significantly lowered the mortality rate (24.1%, versus 48.4% in patients receiving CS

alone) ($P < 0.01$). This significant difference was not found in our previous analyses of various populations and might be the consequence of the overrepresentation of severe renal symptoms in the MPA patients included in this study. It is pertinent to note that, despite a higher number of patients with severe disease in the CS and cytotoxic drug treatment group, mortality was lower. PE was prescribed to patients with more severe disease, which could explain the higher number of deaths in this group. PE was not able to lower the number of relapses. Based on the FFS, renal involvement was associated with higher mortality, and the results of this study indicate that the most severe renal manifestations should be treated with CS and cytotoxic agents. Conversely, when PAN, Churg-Strauss syndrome, and MPA were considered together, independent of prognostic factors, the mortality rates were comparable for patients treated with and those not teated with cytotoxic drugs.

For the first time, 2 scoring systems were applied at the time of the initial manifestations, and their contributions were compared. The FFS has been prospectively validated (13), and the BVAS was recently described as a score that is able to predict disease evolution (14). The 2 scores were correlated, but each had its own specificities. To establish prognosis at the time of the first manifestation, the FFS proved superior to the BVAS. It is also easier to use and better adapted to a disease whose prognosis, in the majority of cases, reflects renal involvement. Conversely, the BVAS, which is more complicated but also more detailed with multiple items, could be a better predictor of remission. This study brings to light the individual contributions of the 2 scoring systems, which should be applied in treatment decisions.

In MPA, similar to other vasculitides (13), death can result from disease activity or various causes not necessarily related to the vasculitis, but also from infections that are the consequence of treatment. The study also showed that a few patients with the symptoms of MPA had microaneurysms and/or stenoses that reflect involvement of medium-sized arteries; these events are usually characteristic of PAN. This observation indicates a certain overlap of features between MPA and PAN. In an autopsy series, Inoue et al observed that microaneurysms were localized in the interlobular arteries of the kidneys (27). Nevertheless, to discern more clear-cut characteristics of MPA, we suggest considering the presence of renal infarcts, microaneurysms, and/or stenoses as diagnostic for PAN and exclusionary for MPA, except when the patient has clearly established symptoms of MPA, such as GN or alveolar hemorrhage. This approach would restrict the scope of MPA, but would not completely exclude overlap diseases.

The presence of ANCA and the absence of microaneurysms and/or stenoses should be used as criteria for the diagnosis of MPA. In addition to the clinical manifestations considered characteristic of MPA, such as GN or lung hemorrhage, immunologic and angiographic findings can help the clinician make a precise diagnosis. However, at present, they cannot predict, but can orient, therapeutic strategies. Patients with MPA should be treated according to their prognostic factors (13) so as to neither overtreat mild disease nor undertreat severe disease (28).

REFERENCES

1. Davson J, Ball J, Platt R. The kidney in periarteritis nodosa. QJM 1948;17:175–202.
2. Jennette C, Falk RJ, Andrassy K, Bacon PA, Churg J, Gross WL, et al. Nomenclature of systemic vasculitides: proposal of an international consensus conference. Arthritis Rheum 1994;37:187–92.
3. Watts RA, Jolliffe VA, Carruthers DM, Lockwood M, Scott DGI. Effect of classification on the incidence of polyarteritis nodosa and microscopic polyangiitis. Arthritis Rheum 1996;39:1208–12.
4. Guillevin L, Jarrousse B, Lok C, Lhote F, Jais JP, Du DLTH, et al, and the Cooperative Study Group for Polyarteritis Nodosa. Long-term followup after treatment of polyarteritis nodosa and Churg-Strauss angiitis with comparison of steroids, plasma exchange and cyclophosphamide to steroids and plasma exchange: a prospective randomized trial of 71 patients. J Rheumatol 1991;18:567–74.
5. Guillevin L, Fain O, Lhote F, Jarrousse B, Huong DLT, Bussel A, et al. Lack of superiority of steroids plus plasma exchange to steroids alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome: a prospective, randomized trial in 78 patients. Arthritis Rheum 1992;35:208–15.
6. Guillevin L, Lhote F, Jarrousse B, Fain O. Treatment of polyarteritis nodosa and Churg-Strauss syndrome: a meta-analysis of 3 prospective controlled trials including 182 patients over 12 years. Ann Med Interne (Paris) 1992;143:405–16.
7. Guillevin L, Lhote F, Sauvaget F, Deblois P, Rossi F, Levallois D, et al. Treatment of polyarteritis nodosa related to hepatitis B virus with interferon-alpha and plasma exchanges. Ann Rheum Dis 1994;53:334–7.
8. Guillevin L, Lhote F, Cohen P, Jarrousse B, Lortholary O, Généreau T, et al. Corticosteroids plus pulse cyclophosphamide and plasma exchanges versus corticosteroids plus pulse cyclophosphamide alone in the treatment of polyarteritis nodosa and Churg-Strauss syndrome patients with factors predicting poor prognosis: a prospective, randomized trial in sixty-two patients. Arthritis Rheum 1995;38:1638–45.
9. Guillevin L, Cordier J-F, Lhote F, Cohen P, Jarrousse B, Royer I, et al. A prospective, multicenter, randomized trial comparing steroids and pulse cyclophosphamide versus steroids and oral cyclophosphamide in the treatment of generalized Wegener's granulomatosis. Arthritis Rheum 1997;40:2187–98.
10. Guillevin L, Lhote F, Amouroux J, Ghérardi R, Callard P, Casassus P. Antineutrophil cytoplasmic antibodies, abnormal angiograms and pathological findings in polyarteritis nodosa and Churg-Strauss syndrome: indications for the classification of vasculitides of the Polyarteritis Nodosa Group. Br J Rheumatol 1996;35:958–64.

11. Hagen C, Daha MR, Hermans J, Andrassy K, Csernok E, et al. Diagnostic value of standardized assays for antineutrophil cytoplasmic antibodies in idiopathic systemic vasculitis. Kidney Int 1998;53:747–53.
12. Jarrousse B, Guillevin L, Bindi P, Hachulla E, LeClerc P, Nilson B. Increased risk of Pneumocystis carinii pneumonia in patients with Wegener's granulomatosis. Clin Exp Rheumatol 1993;11:615–21.
13. Guillevin L, Lhote F, Gayraud M, Cohen P, Jarrousse B, Lortholay O, et al. Prognostic factors in polyarteritis nodosa and Churg-Strauss syndrome: a prospective study in 342 patients. Medicine (Baltimore) 1996;75:17–28.
14. Luqmani R, Exley A, Kitas G, Bacon P. Disease assessment and management of the vasculitides. Bailleres Clin Rheumatol 1997; 11:423–46.
15. Kaplan E, Meier P. Nonparametric estimation for incomplete information. J Am Stat Assoc 1958;53:457–81.
16. Peto R, Pike M, Armitage P. Design and analysis of randomized clinical trials requiring prolonged observations of each patient. II. Analysis and examples. Br J Cancer 1977;35:1–39.
17. Wohlwill F. Uber die nur Mikroskopisch erkenbarre Form der Periarteritis nodosa. Arch Pathol Anat 1923;246:377–411.
18. Küssmaul A, Maier K. Ueber eine nicht bisher beschreibene eigenthümliche Arterienerkrankung (Periarteritis Nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskelhämung einhergeht. Dtsch Arch Klin Med 1866;1:484–518.
19. Savage C, Winearls C, Evans D, Rees A, Lockwood C. Microscopic polyarteritis: presentation, pathology and prognosis. QJM 1985;56:467–83.
20. Adu D, Howie A, Scott D, Bacon PA, McGonigle RJS, Michael J. Polyarteritis nodosa and the kidney. QJM 1987;62:221–37.
21. Serra A, Cameron J, Turner D, Hartley B, Ogg CS, Neild GH. Vasculitis affecting the kidney: presentation, histopathology and long-term outcome. QJM 1984;53:181–207.
22. Schnabel A, Reuter M, Gross W. Significance of low-grade alveolar bleeding in ANCA-associated vasculitides (abstract). Clin Exp Immunol 1998;112:S65.
23. Jennette JC, Wilkman AS, Falk RJ. Anti-neutrophil cytoplasmic autoantibody-associated glomerulonephritis and vasculitis. Am J Pathol 1989;135:921–30.
24. Guillevin L, Lhote F, Brauner M, Casassus P. Antineutrophil cytoplasmic antibodies (ANCA) and abnormal angiograms in polyarteritis nodosa and Churg-Strauss syndrome: indications for the diagnosis of microscopic polyangiitis. Ann Med Interne (Paris) 1995;146:548–50.
25. Gayraud M, Guillevin L, Cohen P, Lhote F, Cacoub P, Deblois P, et al. Treatment of good-prognosis polyarteritis nodosa and Churg-Strauss syndrome: comparison of steroids and oral or pulse cyclophosphamide in 25 patients. Br J Rheumatol 1997;36:1290–7.
26. Gordon M, Luqmani RA, Adu D, Greaves I, Richards N, Michael J, et al. Relapses in patients with a systemic vasculitis. QJM 1993;86:779–89.
27. Inoue M, Akikusa B, Masuda Y, Kondo Y. Demonstration of microaneurysms of the interlobular arteries of the kidneys in microscopic polyangiitis: a three-dimensional study. Hum Pathol 1998;29:223–7.
28. Jennette J, Falk R. Small-vessel vasculitis. N Engl J Med 1997; 337:1512–23.

APPENDIX A: THE COOPERATIVE STUDY GROUP FOR POLYARTERITIS NODOSA

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