Renal Involvement in Churg-Strauss Syndrome

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• ***Background:*** **Churg-Strauss syndrome (CSS) is a rare disorder characterized by asthma, eosinophilia, and systemic vasculitis. Renal involvement is not regarded as a prominent feature, and its prevalence and severity vary widely in published reports that usually refer to small series of selected patients.** ***Methods:*** **We examined the prevalence, clinicopathologic features, and prognosis of renal disease in 116 patients with CSS.** ***Results:*** **There were 48 men and 68 women with a mean age of 51.9 years (range, 18 to 86 years). Signs of renal abnormalities were present in 31 patients (26.7%). Rapidly progressive renal insufficiency was documented in 16 patients (13.8%); urinary abnormalities, 14 patients (12.1%); and chronic renal impairment, 1 patient. There were 3 additional cases of obstructive uropathy. Sixteen patients underwent renal biopsy, which showed necrotizing crescentic glomerulonephritis in 11 patients. Other diagnoses were eosinophilic interstitial nephritis, mesangial glomerulonephritis, and focal sclerosis. Antineutrophil cytoplasmic antibody (ANCA) was positive in 21 of 28 patients (75.0%) with nephropathy versus 19 of 74 patients without (25.7%; $P < 0.001$). In particular, all patients with necrotizing crescentic glomerulonephritis were ANCA positive. After a median follow-up of 4.5 years, 10 patients died (5 patients with nephropathy) and 7 patients developed mild chronic renal insufficiency. Five-year mortality rates were 11.7% (95% confidence interval, 3.9 to 33.3) in patients with nephropathy and 2.7% (95% confidence interval, 0.7 to 10.7) in those without ($P = 0.10$).** ***Conclusion:*** **Renal abnormalities are present in about one quarter of patients with CSS. The prevailing picture is ANCA-associated necrotizing crescentic glomerulonephritis; however, other forms of nephropathy also may occur. Outcome and long-term follow-up usually are good.** ***Am J Kidney Dis*** **47:770-779.**

INDEX WORDS: Churg-Strauss syndrome; vasculitis; antineutrophil cytoplasmic antibody (ANCA); necrotizing crescentic glomerulonephritis; antineutrophil cytoplasmic antibody–associated vasculitis.

CHURG-STRAUSS SYNDROME (CSS) is defined as an eosinophil-rich and granulomatous inflammation involving the respiratory tract and necrotizing vasculitis affecting small- to medium-sized vessels, associated with asthma and eosinophilia.[1,2]

Pathological confirmation is based on the presence of extravascular granulomas in association with necrosis and predominant extravascular eosinophils, as well as necrotizing vasculitis,[1,2] but all these lesions rarely are found together in biopsy specimens.[3-6] Therefore, clinical criteria for diagnosis have been proposed.[3]

The vast majority of patients have blood eosinophilia (>1,500 eosinophils/μL or >10%), with exceptions represented by those previously treated with corticosteroids for asthma.[4,6-8]

Approximately 50% of patients are antineutrophil cytoplasmic antibody (ANCA) positive, most with a perinuclear pattern (P-ANCA) with antigen specificity for myeloperoxidase (MPO-ANCA).[5] Because of this and other similarities, CSS is classified among the so-called ANCA-associated systemic vasculitides.[2,9-10]

To date, the prevalence and severity of renal involvement in patients with CSS is not well characterized. The reported prevalence of renal involvement in patients with CSS varies widely, ranging from less than 20% to 88%, probably

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because of patient selection bias, varying criteria used for renal disease definition, and small numbers of case series published to date.[1,3-5,7,8,11-15] In addition, the prevalence of each type of renal involvement is not known. Renal disease usually was described as a mild form of focal and segmental necrotizing glomerulonephritis, and it is not considered a major feature of this disease.[5,6] However, sometimes patients develop a severe form of rapidly progressive glomerulonephritis.[13,16-22] In addition to intrinsic renal disease, renal dysfunction also may result from obstructive uropathy caused by vasculitic involvement of the ureters and lower genitourinary tract.[23-26]

The aim of our work is to examine the prevalence, clinicopathologic features, and outcome of renal involvement in a large cohort of patients with CSS attending the internal medicine and medical specialties departments of 4 regional hospitals.

METHODS

Patients

We retrospectively examined medical records of 116 patients with a clinical diagnosis of CSS attending the internal medicine departments (nephrology, clinical immunology, and rheumatology; pneumology; neurology; and others) of 4 general hospitals in northern Italy between 1985 and 2004.

CSS is defined according to Chapel Hill Consensus Conference nomenclature.[2] Classification criteria for CSS of the American College of Rheumatology (ACR)[27] and Lanham (Hammersmith) criteria[3] were applied retrospectively to the study population.

Extrarenal organ system involvement was assessed by using the Birmingham Vasculitis Activity Score (BVAS) item list.[28] The Disease Extent Index (DEI) and prognostic Five Factor Score (FFS) also were calculated according to the respective investigators.[29,30]

Biochemical and Serological Markers

Routine laboratory tests were performed in all patients at the time of diagnosis and at follow up.

ANCA status was determined at the time of diagnosis (before immunosuppressive treatment) in 102 patients by using indirect immunofluorescence and antigen-specific proteinase 3 (PR3) and MPO enzyme-linked immunosorbent assay, as previously described.[31,32] ANCA serological tests were performed first in each hospital and rechecked centrally on frozen serum samples in the laboratory of San Carlo Borromeo Hospital in Milan, which participated in the European Commission/Community Bureau of Reference study for ANCA assay standardization.[33]

Definitions and Pathological Studies

Renal abnormalities are defined as the presence of renal insufficiency (serum creatinine $>$ 1.4 mg/dL [$>$124 μmol/L]) and/or urinary abnormalities (proteinuria with protein $>$ 0.3 g/d and microscopic hematuria with $\geq$10 erythrocytes/high-power field on 2 separate occasions in the absence of urinary infection).

A renal biopsy was performed when judged necessary by physicians taking care of the patients.

Light microscopy slides were prepared and stained according to standard methods for light and immunofluorescence microscopy.[34]

A patient was considered to be in full remission when there was complete absence of clinical disease activity for at least 6 months by using the BVAS item list, with the exception of asthma or neurological sequelae.[4]

The nephropathy was considered to be in remission when there was stabilization or improvement in renal function in combination with the absence of glomerular erythrocyturia and red blood cell casts.[35,36]

Relapse is defined as the occurrence or recurrence of a clinical manifestation attributable to CSS. Persistent asthma or an isolated increase in eosinophilia is not considered a relapse.[4]

A renal flare is defined as the occurrence or recurrence of renal impairment (increase in serum creatinine of $>$ 30% within 3 months) in association with microscopic erythrocyturia and proteinuria.[35,36]

Treatment

All patients were treated with corticosteroids (1 mg/kg/d for 3 to 4 weeks, with subsequent tapering). Cyclophosphamide (daily oral or pulses), as induction treatment, was added for 3 to 6 months in 49 patients (42.2%), usually the most severe cases.[35,37] Methylprednisolone pulses (0.5 to 1 g/d for 3 consecutive days) were administered to 26 patients, and plasma exchange was performed in 5 patients. Intravenous immunoglobulins, methotrexate, and azathioprine were added in 1, 5, and 1 patient, respectively. Treatment during remission consisted of corticosteroids (5 to 15 mg/d), in association with azathioprine in 15 patients, methotrexate in 12 patients, and cyclosporine A in 7 patients. Two or more additional immunosuppressive drugs were used in 4 patients.

Long-term follow-up and outcome were established after the patient's last visit or death.

Statistical Analysis

All analyses were performed using Stata Statistical Software Release 9.0 (StataCorp, College Station, TX; 2005). Differences between groups in continuous variables were tested by using Mann-Whitney test, and in categorical variables, by using Fisher exact test. Cumulative risk for death was estimated by means of the life-table (actuarial) method because survival times were recorded at yearly intervals and therefore individual times at which death (or censoring) occurred were not precisely known. The difference in risk for death was examined by using the likelihood ratio test. The Stata program ltable was used for computation. All

reported *P* are 2 sided. *P* less than 0.05 is regarded as statistically significant.

RESULTS

Clinical and Histological Characteristics

There were 48 men and 68 women with a median age of 52 years (range, 18 to 86 years). All except 4 patients had bronchial asthma, which usually preceded the diagnosis of CSS. Eosinophilia (eosinophils > 10%) was present in 111 patients, with the exception of 5 patients previously administered steroids for asthma. Of 116 patients with CSS, 106 patients (91.4%) met the ACR classification criteria for CSS; 100 patients (86.2%) met Lanham criteria, and 113 patients (97.4%) met at least 1 of the 2. ANCA was positive by means of immunofluorescence in 40 of 102 patients (39.2%) tested at the time of diagnosis. A P-ANCA pattern was found in 32 of 40 patients (80.0%), with specificity for MPO in 29 patients, whereas a cytoplasmic pattern (C-ANCA), with specificity for PR3, was found in 3 of 40 patients (7.5%). Three P-ANCA–positive samples were negative by means of enzyme-linked immunosorbent assay. Atypical patterns (P + C) were found in 5 patients (12.5%) with anti-MPO antibodies by using enzyme-linked immunosorbent assay. Results obtained in the reference laboratory confirmed, in terms of positivity/negativity, results obtained locally (data not shown).

Renal abnormalities, as previously defined, were present in 31 patients (26.7%). Tables 1 and 2 list the main characteristics of renal involvement in these patients. Sixteen patients (13.8%) had a clinical picture of rapidly progressive or acute renal insufficiency (patients 1, 2, 4, 6, 8, 10, 11, 12, 15, 19, 23, 25, 27, 29, 30, and 31), 14 patients (12.1%) had isolated urinary abnormalities (patients 3, 5, 7, 9, 13, 17, 18, 20, 21, 22, 24, 26, 28, and 31), and 1 patient (0.9%) had mild chronic renal impairment (patient 14). Three additional patients (1 patient, macroscopic hematuria; 2 patients, asymptomatic) had obstructive uropathy caused by ureteral stenosis, bilateral in 1 patient (patients 33 to 35).

Sixteen patients (9 patients, acute or rapidly progressive renal insufficiency; 5 patients, isolated urinary abnormalities; 1 patient, mild chronic

Table 1. Main Clinical, Laboratory, and Histological Data for Patients With Renal Involvement Who Underwent Renal Biopsy

Patient No.	Age (y)/ Sex	ACR*	Serum Creatinine (mg/dL)	Hematuria	Proteinuria (g/d)	ANCA	Histology	Crescent (%)	Eosin	Therapy	Follow-Up (y)	Outcome (serum creatinine; mg/dL)
1	45/F	Yes	6.2	+++	1.30	P/MPO	NCGN	67	−	Pd + Cy	7.0	0.8
2	56/F	No	1.7	+++	0.40	P/MPO	NCGN	5	−	Pd + Az	8.0	1.3
3	65/F	Yes	0.9	+++	0.40	P/MPO	NCGN	32	−	Pd + Cy	11.0	1.3
4	29/F	Yes	1.8	++	4.00	P/MPO	NCGN	30	−	Pd + Cy	4.0	0.9
5	69/F	Yes	0.7	++	0.50	P/MPO	NCGN	7	−	Pd	4.0	0.8
6	66/F	Yes	2.8	+++	1.00	P + C/MPO	NCGN	55	−	Pd + Cy	1.5	2.5
7	47/M	Yes	0.7	+	0.38	P + C/MPO	NCGN	11	+	Pd	0.8	0.7
8	86/M	Yes	5.0	+++	1.80	C/PR3	NCGN	60	−	Pd	3.0	Hemodialysis†
9	51/M	Yes	0.9	+++	0.55	C/PR3	NCGN	15	−	Pd + Cy	4.0	1.1
10	51/M	Yes	5.7	+++	2.50	P/MPO	NCGN + TIN	62	++	Pd	2.2	1.3
11	40/M	Yes	2.3	++	1.20	P/MPO	NCGN + TIN	30	++	Pd + Cy	7.0	1.1
12	77/F	Yes	3.3	++	0.35	C/PR3	TIN	0	++	P + Az	4.0	2.1
13	38/F	Yes	1.0	+	1.00	Negative	FPGN	0	−	Pd + Cy	14.0	1.3
14	73/F	Yes	1.5	−	0.70	Negative	FSGS‡	0	−	Pd	1.6	1.5
15	22/M	Yes	7.0§	−	+	ND	Normal‖	0	−	Pd + Cy	19.0	1.2¶
16	44/F	Yes	0.9	++	0.09	Negative	Normal	0	−	Pd	5.0	1.0

NOTE. The grey area highlights patients without NCGN. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.

Abbreviations: C, cytoplasmic ANCA; PR3, anti-PR3–positive ANCA; NCGN, necrotizing crescentic glomerulonephritis; FPGN, focal proliferative glomerulonephritis; TIN, tubulointerstitial nephritis; FSGS, focal segmental glomerular sclerosis; eosin, eosinophil-rich interstitial infiltrate; Pd, prednisone; Cy, cyclophosphamide; Az, azathioprine.

*At least 4 of 6 criteria present.

†Died of pulmonary hemorrhage.

‡Previously diagnosed.

§Acute renal failure caused by bilateral ureteral stenosis.

‖Mild interstitial lymphohistiocytic and plasma cell infiltrates (ureteral stenosis).

¶After surgery.

Table 2. Main Clinical and Laboratory Data for Patients With Renal Involvement Who Did Not Undergo Renal Biopsy

Patient No.	Age (y)/Sex	ACR*	Serum Creatinine (mg/dL)	Hematuria	Proteinuria (g/d)	ANCA	Therapy	Follow-Up (y)	Outcome (serum creatinine; mg/dL)
17	58/M	Yes	0.8	++	0.40	P + C/MPO	Pd + Cy	6.5	1.3
18	45/F	Yes	1.0	+++	0.54	P/MPO	Pd + Cy	2	0.8
19	75/M	Yes	7.0†	+++	1.30	P/MPO	Pd	0.5	3.0‡
20	60/M	Yes	1.0	+	1.20	P + C/MPO	Pd + Cy	0.5	1.2
21	44/F	Yes	0.9	++	0.60	P/MPO	Pd + Cy	1.5	0.7
22	40/M	Yes	1.1	+	0.42	P/MPO	Pd + Cy	3.5	1.0
23	78/F	No	2.7	++	1.20	ND	Pd	9	1.3§
24	35/F	Yes	0.8	+	0.50	ND	Pd + Cy	12.0	0.9
25	79/M	Yes	2.8	++	0.70	Negative	Pd	0.5	1.8
26	43/F	Yes	0.7	+	0.40	Negative	Pd	17	0.9
27	63/F	Yes	2.3	+	++	Negative	Pd	4	1.1
28	41/F	Yes	0.8	+	0.44	Negative	Pd	7	0.7
29	69/M	Yes	2.1	+	0.27	Negative	Pd + Cy	7	‖
30	62/M	Yes	7.5	++	0.22	P/MPO	Pd + Cy	0.2	2.8‡
31	48/F	Yes	0.8	+	0.30	P/MPO	Pd + Cy	0.2	0.7
32	61/M	Yes	3.9°	Macroscopic	0.50	P/MPO	Pd	1.2	1.4
33	64/F	Yes	1.1¶	Macroscopic	−	Negative	Pd + MT	7	1.3
34	45/M	No	1.1#	−	−	P/MPO	Pd	6.8	1.0
35	46/F	Yes	0.9#	−	−	Negative	Pd	0.5	1.1

NOTE. The grey area highlights patients with obstructive uropathy. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4.

Abbreviations: C, cytoplasmic ANCA; PR3, anti-PR3–positive ANCA; ND, not determined; Cy, cyclophosphamide; MT, methotrexate; Pd, prednisone.

*At least 4 of 6 criteria present.

†In a single kidney.

‡Died of infection.

§Died of senile decay.

‖Died of myocardial infarct.

¶Bilateral obstructive uropathy.

#Monolateral obstructive uropathy.

renal impairment; and 1 patient, persistent isolated microscopic hematuria) underwent a renal biopsy (Table 1).

All renal biopsies were performed at the time of diagnosis of CSS, with the exception of the patient with isolated microscopic hematuria, who underwent renal biopsy 3 years after diagnosis because of persistence of hematuria despite clinical extrarenal remission.

Eleven biopsies showed a histological picture of pauci-immune focal necrotizing glomerulonephritis (Table 1; patients 1 to 11). Extracapillary proliferation in more than 50% of glomeruli was present in 4 patients (nos. 1, 6, 8, and 10), all with a clinical picture of rapidly progressive glomerulonephritis. Percentage of crescents varied from 5% to 32% in the other patients. An eosinophilic-rich interstitial infiltrate was present in 3 patients (nos. 7, 10, and 11), 2 of whom had associated tubulointerstitial nephritis (patients 10 and 11). Two patients also had necrotizing vasculitis of a medium-sized intrarenal artery.

One biopsy in a patient with acute renal impairment showed eosinophil-rich interstitial infiltrates without glomerular involvement (patient 12).

Focal proliferative mesangial glomerulonephritis, without necrosis and extracapillary proliferation, was found in a patient with persistent isolated urinary abnormalities (patient 13), and focal segmental sclerosis was found in another patient with a previous long-standing history of mild chronic renal impairment, preceding the apparent clinical onset of the disease (patient 14). Neither patient had immune deposits at immunofluorescence.

The patient with persistent isolated microscopic hematuria had normal findings at both light and immunofluorescence microscopy, whereas elec-

tron microscopic examination showed segmental thinning of the glomerular basement membrane (patient 16).

Mild interstitial nephritis in the absence of glomerular lesions was noted in a patient with acute renal failure caused by bilateral ureteral stenosis (patient 15). In this patient, the kidney biopsy specimen was obtained during surgery for bilateral ureteral stenosis.

The 11 patients with histologically proven necrotizing crescentic glomerulonephritis were ANCA positive versus only 19 of 74 patients (25.7%) without renal involvement ($P < 0.001$). A P-ANCA pattern, by means of indirect immunofluorescence, with specificity for MPO was found in 7, a C-ANCA pattern with specificity for PR3 was found in 2 patients, and an atypical (P + C) pattern (anti-MPO positive) was found in 2 patients.

Sixteen patients with signs of renal abnormalities (7 patients, renal impairment; 9 patients, urinary abnormalities) did not undergo renal biopsy for several reasons (Table 2): (1) acute renal failure in a single kidney (patients 19 and 32); extrarenal clinical picture requiring maximal therapy (patients 17, 18, 20, 21, 22, and 29); age (patients 23 and 25); transitory mild urinary abnormalities (patients 24, 26, 28, and 31); contraindications (patient 27); and patient refusal (patient 30).

Three additional patients had obstructive uropathy, which was bilateral in 1 patient. The clinical picture in these patients was heterogeneous, ranging from absence of urinary abnormalities to macroscopic hematuria in the patient with bilateral ureteral stenosis.

Nine of 14 patients (64.3%) with clinical renal involvement, tested at the time of diagnosis, were ANCA positive. Seven patients had a P-ANCA pattern with specificity for MPO, and 2 patients had an atypical (P + C) ANCA pattern with antibodies to MPO by using enzyme-linked immunosorbent assay (Table 2). One of 3 patients with obstructive uropathy also was P-ANCA/MPO-ANCA positive (Table 2).

When patients with biopsy-proven nephropathy were pooled with patients with clinical renal abnormalities who did not undergo kidney biopsy, excluding those with obstructive uropathy, ANCA was positive in 21 of 28 patients (75.0%) tested versus 19 of 74 patients (25.7%) without kidney involvement ($P < 0.001$; Table 3).

No significant differences in other clinical or laboratory parameters between these 2 groups

Table 3. Main Clinical Features in Patients With or Without Renal Involvement

	Renal Disease* (n = 30)	No Renal Disease (n = 86)	*P*
Age (y)	57 (25-86)	51 (18-77)	0.10
Asthma	29 (96.7)	83 (96.5)	1.00
Constitutional symptoms	27 (90.0)	49 (57.0)	0.001
Rhinitis	23 (76.7)	61 (70.1)	0.64
Sinusitis	26 (86.7)	63 (73.3)	0.21
Skin involvement	18 (60.0)	40 (46.5)	0.67
Lung involvement	14 (46.7)	43 (50.0)	0.83
Heart involvement	5 (16.7)	13 (15.1)	0.77
Gastrointestinal involvement	2 (6.7)	23 (26.7)	0.021
Peripheral neuropathy	18 (60.0)	58 (67.4)	0.51
Central nervous system involvement	5 (16.7)	13 (15.1)	0.78
ACR criteria	28 (93.3)	78 (90.7)	1.00
Lanham criteria	26 (86.7)	74 (86.0)	1.00
Eosinophil (/μL)	5,229 (1,440-18,866)	4,100 (600-28,815)	0.48
ANCA positive	21/28 (75.0)	19/74 (25.7)	<0.001
BVAS	26 (13-40)	19 (6-40)	<0.001
DEI	7 (3-11)	6 (2-10)	<0.001
FFS ≥ 2	16 (53.3)	5 (5.8)	<0.001

NOTE. Categorical variables reported as number (percent), and continuous variables are reported as median (range). *P* refers to Fisher exact test for categorical variables and Mann-Whitney test for continuous variables.

*Patients with obstructive uropathy were not considered in this subgroup because they were not affected by intrinsic renal disease. A patient (no. 14; Table 1) was not included among patients with renal involvement because the nephropathy preceded by several years the onset of CSS and was considered not to be related to CSS.

were detected, except for constitutional symptoms, which were more frequent in patients with renal disease (90.0% versus 57.0%; $P = 0.001$), and gastrointestinal involvement, which was more frequent in patients without nephropathy (6.7% versus 26.3%; $P = 0.021$; Table 3).

BVAS and DEI score were significantly higher in patients with renal abnormalities (median, 26 versus 19 and 7 versus 6, respectively; $P < 0.001$). When the score attributed to the kidney was subtracted from the total score, such differences were no longer detectable (data not shown).

As expected, an FFS of 2 or higher also was significantly more frequent in patients with renal disease (Table 3).

All patients with renal involvement were treated with corticosteroids, in association with immunosuppressive drugs (usually cyclophosphamide) in most of them (Tables 1 and 2).

It was not possible to evaluate the relative efficacy of the association of corticosteroids plus cyclophosphamide versus corticosteroids alone because the 2 groups were not similar. Starting serum creatinine levels were not different (2.3 ± 2.3 mg/dL [203 ± 203 μmol/L] in patients treated with cyclophosphamide versus 2.4 ± 2.1 mg/dL [212 ± 186 μmol/L] in patients treated with corticosteroids alone), and median age of patients treated with corticosteroids alone was older than that of patients treated with the combination of corticosteroids plus cyclophosphamide (61.0 years; range, 41.0 to 86.0 years versus 45.0 years; range, 22.0 to 69.0 years; $P = 0.03$). Nevertheless, there was a trend toward lower serum creatinine levels at the end of the follow-up in patients treated with cyclophosphamide (1.2 ± 0.6 mg/dL [106 ± 53 μmol/L] versus 1.8 ± 2.3 mg/dL [159 ± 203 μmol/L]; $P = 0.31$). The temporal profile of response to treatment was not different in the 2 groups, with most patients reaching remission in 3 to 6 months.

After a median follow-up of 4.5 years (range, 6 months to 20 years), 10 patients (5 patients with renal involvement) died; the only patient who underwent long-term dialysis treatment eventually died of pulmonary hemorrhage. Five-year mortality rates were 11.7% (95% confidence interval, 3.9 to 33.3) in patients with renal abnormalities and 2.7% (95% confidence interval, 0.7 to 10.7) in those without ($P = 0.10$).

Thirteen patients (11.2%), 3 patients with renal involvement, were lost to follow-up after a median of 3.0 years (range, 1 to 6 years). They were included in survival analysis until the last visit.

At the end of follow-up, 7 patients had mild chronic renal insufficiency; none showed a doubling of serum creatinine level. Renal flares were never recorded during follow-up, whereas extrarenal flares occurred in 28.4% of patients.

DISCUSSION

This is the first study that systematically investigates the prevalence, presentation, and clinical course of renal involvement in a large cohort of patients with CSS.

We tried to minimize selection bias of patients in our study by enrolling patients from different medical departments (internal medicine, nephrology, clinical immunology and rheumatology, pneumology, and neurology units) of 4 large general hospitals from northern Italy.

Renal disease was present in about one quarter of patients with CSS. Most patients had renal insufficiency and/or significant urinary abnormalities. Rare patients had monolateral and bilateral obstructive uropathy at diagnosis.

The main histological picture was of necrotizing crescentic glomerulonephritis, but other forms of nephropathy also were detected. Patients with renal involvement and especially patients with necrotizing crescentic glomerulonephritis often were ANCA positive.

This prevalence of renal abnormalities is in line with those of the largest series published in recent years. Guillevein et al[4] reported that renal disease, defined as the presence of proteinuria with protein of 1 g/d or greater, microscopic hematuria, and/or histological findings in a renal biopsy consistent with systemic vasculitis, was present at onset in 26% of 96 patients. Keogh and Specks[8] reported that renal involvement, not further specified, was present in 25% of 91 patients.

All patients classified as having renal disease showed a clinical picture suggestive of renal involvement at the time of diagnosis, whereas no patient without such picture developed renal involvement thereafter. The prevailing clinical picture at onset was either mild urinary abnormali-

ties or rapidly progressive renal insufficiency, as described in most series.[1,3-5,7,8,11-15]

Kidney biopsy was performed in approximately half the patients with renal abnormalities. A pauci-immune necrotizing crescentic form of glomerulonephritis was found in the vast majority of patients. Interstitial eosinophil-rich infiltrate was present in 3 patients. Two patients had associated tubulointerstitial nephritis, and a patient showed eosinophilic tubulointerstitial nephritis without glomerular involvement. Focal mesangial proliferative glomerulonephritis, without immune deposits, was found in a patient with microscopic hematuria and proteinuria. The same histological pattern was still present a few years later when a repeated biopsy was performed because of persistent urinary abnormalities (data not shown). Two patients showed a normal picture at kidney biopsy. One of these patients had isolated microscopic hematuria that persisted in follow-up, and the other patient had acute renal failure caused by obstructive uropathy.

There are very few descriptions of renal histological findings in patients with CSS, with most of them in the form of case reports.[16-19,21] Our data show that the most frequent lesion is a focal segmental form of necrotizing crescentic glomerulonephritis, resembling that found in other ANCA-associated vasculitides, with arteritis and eosinophil infiltration (a distinctive feature) in a minority of patients.[11,20,22]

As reported by others,[11,38] we found histological pictures of mesangial proliferative glomerulonephritis, focal glomerular sclerosis, and eosinophilic tubulointerstitial nephritis in a few patients only. In these patients, clinical signs of renal involvement usually were less severe. The possibility of obstructive uropathy caused by vasculitic involvement of the ureters or urogenital tract also was shown in our series of patients, as described in single cases.[23-26]

We found ANCAs in approximately 40% of our population, which is in the range (35% to 77%) previously reported in smaller series.[4,7,8,14,15] P-ANCA, with specificity for MPO, was the main fluoroscopic pattern (~three fourths of cases), as described by most.

Patients with necrotizing crescentic glomerulonephritis and, in general, patients with clinical signs of glomerular involvement, had a statistically significant greater prevalence of ANCA positivity. Worthy of note is that most (if not all) case reports of necrotizing crescentic glomerulonephritis in patients with CSS[16-19,21] showed ANCA positivity (usually P-ANCA/MPO-ANCA), as in our cohort. Moreover, results of small series of patients suggested that MPO-ANCA may be associated with the onset of glomerular disorder in patients with CSS.[20,22] Guillevein et al[4] sought ANCA in sera of 42 patients at the time of diagnosis. ANCA was detected by using indirect immunofluorescence in 20 of 42 patients (47.6%), a percentage similar to ours. They reported the fluorescent pattern to be perinuclear in 15 patients, cytoplasmic in 1 patient, and unspecified in 4 patients. ANCA specificity, determined by using enzyme-linked immunosorbent assay in 11 patients, was anti-MPO in 10 patients and not specified in 1 patient. No details were given on the clinical association of ANCA positivity, although histologically proven rapidly progressive necrotizing glomerulonephritis was documented in 3 patients only.[4] More recently, the same group reported in abstract form that ANCA was detected in 43 of 112 patients (38%) with ANCA positivity at diagnosis associated with a significantly greater frequency of renal involvement.[39] In addition, in a retrospective multicenter study of ANCA-associated renal vasculitis, Booth et al[40] found that ANCA was present in 92% of 256 patients, including most of the 11 patients with CSS. Another group found that central nervous system involvement was the only clinical manifestation that correlated with ANCA status.[8] However, only 30 of 91 patients were tested at the time of diagnosis before treatment, and details about renal disease definition and renal histological characteristics were not given.[8]

In other smaller series, ANCA was positive in 40% to 85.7%, but because of the paucity of patients, information about the clinical significance of ANCA positivity was not given (reviewed in [5]).

We failed to detect other features, such as demographic data, prevalence and duration of asthma, magnitude of eosinophilia, and extrarenal involvement, capable of distinguishing patients with necrotizing crescentic glomerulonephritis (and/or clinical renal disease) from those without, with the exception of constitutional symptoms and gastrointestinal involvement. Patients with necrotizing crescentic glomerulone-

phritis had a higher BVAS and DEI score at presentation and, as expected, a higher FFS because 2 of 5 FFS items are renal.[30]

In a previous report, we showed that ANCA positivity in patients with CSS was associated with a greater prevalence of renal disease, pulmonary hemorrhage, and, to a lesser extent, other organ-system manifestations (purpura and mononeuritis multiplex), but with a lower frequency of lung and heart disease, and we speculated that clinical manifestations might be caused mainly by eosinophilic infiltrative disease in ANCA-negative patients, whereas the necrotizing vasculitis component might prevail in ANCA-positive patients.[41] On the basis of these results, it was hypothesized that 2 disease subsets might be part of the spectrum of CSS: an ANCA-associated and an ANCA-negative subset.[42] ANCA-positive patients far more frequently had necrotizing glomerulonephritis, purpura, hemorrhagic alveolitis, and mononeuritis multiplex; histopathological characteristics are characterized by small-vessel vasculitis, and pathogenesis possibly is ANCA related.[42] In the ANCA-negative subset, the main clinical manifestations are pulmonary infiltrates, cardiomyopathy, monopolyneuropathy, and eosinophilic gastritis/enteritis; tissue infiltration by eosinophils is the histopathologic hallmark, and release of toxic products from eosinophils might be the main pathogenic mechanism.[42]

There are emerging clinical and in vivo (animal model) observations that provide compelling evidence that ANCA is primarily and directly involved in the pathogenesis of ANCA-associated systemic vasculitis.[43] In particular, 2 different groups of investigators showed that anti-MPO antibodies alone can cause necrotizing crescentic glomerulonephritis and pulmonary hemorrhage in experimental models.[43,44] Our observations are in keeping with the hypothesis that the presence of ANCA in patients with CSS contributes directly to the development of necrotizing glomerulonephritis.

Patients with renal disease, as well as those without, responded well to glucocorticoid treatment, which was combined with immunosuppressants in the most severe cases. Patient survival was good in accordance with results of other recent studies[8,14,15,40,45] showing, in contrast to previous series,[4,7] that CSS does not appear to confer increased mortality.[8] However, 5 of our 10 patients who died had renal involvement, suggesting that nephropathy might entail a poor prognosis.[30,45] Renal survival also was good: only 1 patient reached end-stage renal failure and no patient had a doubling of serum creatinine level after a mean follow-up of about 5 years. Moreover, although 1 or more extrarenal relapses occurred in 28.4% of patients, a percentage similar to that reported by Keogh and Specks,[8] no renal flares could be documented in our cases.

In conclusion: (1) Renal disease is present in 25% to 30% of patients with CSS, which is much less than in the other ANCA-associated vasculitides, such as microscopic polyangiitis and Wegener granulomatosis. (2) Rapidly progressive glomerulonephritis and urinary abnormalities are the main clinical syndromes. (3) A pauci-immune necrotizing crescentic form of glomerulonephritis, which is not distinguishable in most cases from that found in the other ANCA-associated vasculitis, is the prevailing histological pattern. Eosinophil-rich interstitial infiltrates or intrarenal arteritis can be found in a minority of cases. (4) Other histological forms, such as eosinophilic tubulointerstitial nephritis, focal mesangial proliferative glomerulonephritis, and focal segmental glomerular sclerosis, also can be seen. (5) Renal involvement also can be caused by obstructive uropathy caused by vasculitis and/or granulomatous inflammation of the ureters. (6) Patients with necrotizing crescentic glomerulonephritis are ANCA positive, usually with specificity for MPO, as in the other ANCA-associated vasculitides, suggesting that ANCA positivity might be linked with necrotizing capillaritis in patients with CSS (our 7 patients with alveolar hemorrhage were ANCA positive). (7) Renal flares are rare, and long-term prognosis and outcome generally are good.

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