

## Churg–Strauss syndrome: outcome and long-term follow-up of 32 patients

R. Solans, J. A. Bosch, C. Pérez-Bocanegra, A. Selva, P. Huguet<sup>1</sup>, J. Alijotas, R. Orriols<sup>2</sup>, L. Armadans<sup>3</sup> and M. Vilardell

Department of Internal Medicine, <sup>1</sup>Department of Pathology, <sup>2</sup>Department of Pneumology and <sup>3</sup>Department of Preventive Medicine, Vall d'Hebrón University General Hospital, 08035 Barcelona, Spain

### Abstract

**Objectives.** To study the clinical spectrum and evolution of Churg–Strauss syndrome in order to assess the clinicopathological features of the disease, the response to treatment and the long-term outcome.

**Methods.** Thirty-two patients with proven allergic and granulomatous angiitis (Churg–Strauss syndrome) and followed up at a single institution were evaluated. They were recruited between 1977 and 1999 from internal medicine departments. Data were obtained retrospectively from medical files in 15 cases and prospectively, using a standardized form, for the remaining patients.

**Results.** All patients had asthma and hypereosinophilia. The lungs, skin and peripheral nervous system were the organs most frequently involved. Antineutrophil cytoplasmic antibodies with antimyeloperoxidase specificity (MPO-ANCA) were detected in 77.8% of tested patients but they were not useful for monitoring disease activity. Extravascular granulomas were rarely seen in tissue biopsies. Forty per cent of the patients were treated with steroids alone. Immunosuppressive agents were added to the treatment when severe neurological, cardiac or gastrointestinal involvement was present. The outcome and long-term survival were good. Clinical relapse was rare after the first year of therapy. Dysaesthesiae of the distal limbs, neuropathic pain and cardiac failure were the most frequent sequelae.

**Conclusions.** Churg–Strauss syndrome is a rare disorder characterized by hypereosinophilia and systemic vasculitis occurring in patients with asthma and allergic rhinitis. Vasculitis commonly affects the lungs, skin and peripheral nervous system. Outcome and long-term survival is usually good with steroids alone or in combination with immunosuppressive agents. The syndrome has a low mortality rate compared with other systemic vasculitides.

**KEY WORDS:** Churg–Strauss syndrome, Clinicopathological findings, Survival, Long-term follow-up.

In 1951, Churg and Strauss [1] reported a study of 14 cases of a form of disseminated necrotizing vasculitis occurring exclusively among patients with severe asthma, fever and hypereosinophilia. Pathological examination of these patients revealed granulomatous extravascular lesions as well as inflammatory necrotizing arteritis and eosinophilic infiltration. This syndrome was named allergic granulomatosis and angiitis, or Churg–Strauss syndrome (CSS).

In 1977, 30 cases of CSS diagnosed at the Mayo Clinic over the 25-yr period from 1950 to 1974 were reported [2]. All patients had bronchial asthma,

peripheral eosinophilia and systemic vasculitis, as well as necrotizing vasculitis of small arteries and veins, with prominent eosinophilia of vessels and perivascular tissues. However, necrotizing extravascular granulomatosis was present in only 22 cases, and this led to a change in the criteria for the classification of CSS.

In 1984, Lanham *et al.* [3] described 16 patients with CSS and emphasized that the three major histological features (tissue eosinophilia, necrotizing vasculitis and extravascular granulomas) were not present in all cases. These authors described a phasic pattern of CSS: a prodromal phase with allergic disease (allergic rhinitis and/or asthma), a second phase with peripheral and tissue eosinophilia and a final, vasculitic phase with involvement of several systems.

In 1990, the American College of Rheumatology [4] developed the criteria for the classification of CSS.

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Correspondence to: R. Solans Laqué, Medicina Interna, 3<sup>a</sup> pares, Hospital General Universitario Vall d'Hebrón, Vall d'Hebrón 119-129, 08035 Barcelona, Spain.

Six criteria were selected: asthma, eosinophilia >10% on differential white blood cell count, mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrates on chest X-ray, paranasal sinus abnormality, and a biopsy containing a blood vessel with extravascular eosinophils. Four or more of the six criteria are required for a condition to be classified as CSS. Although these criteria were not designed for diagnosis, they were widely used for this purpose. However, they were not adequate for differentiating among the various clinicopathological expressions of small-vessel vasculitis. Understanding of antineutrophil cytoplasmic antibodies (ANCA) provided a new marker for CSS diagnosis, as approximately 70% of patients with CSS have ANCA, usually perinuclear ANCA with antimyeloperoxidase specificity (MPO-ANCA) [5]. In 1994 the Chapel Hill International Consensus Conference [6] defined CSS as a necrotizing vasculitis affecting small- to medium-sized vessels with eosinophil-rich and granulomatous inflammation involving the respiratory tract, with associated asthma and eosinophilia. However, no diagnostic criteria were suggested.

Here we describe 32 patients with Churg–Strauss syndrome diagnosed at our Department of Internal Medicine between 1977 and 1999. We analyse the clinicopathological features of the disease, the response to treatment and the long-term outcome. This is the largest reported series of CSS patients from a European country collected at a single institution.

## Patients and methods

Thirty-two patients with proven Churg–Strauss syndrome, diagnosed according to the criteria of the American College of Rheumatology [4], were included in the study. All patients had asthma, hypereosinophilia and systemic vasculitis. Clinical data of the patients, particularly the initial manifestations and clinical expression of the disease, were collected. Data were obtained retrospectively from medical files in 15 cases and prospectively for the remaining patients, using a standardized form. Routine laboratory tests were performed in all cases at the time of diagnosis. Rheumatoid factor, antinuclear antibodies, cryoglobulins, concentrations of C3 and C4, syphilis serology and markers of hepatitis B and C were also determined. ANCA, detected by means of indirect immunofluorescence techniques on alcohol-fixed normal neutrophils, were tested in all patients from 1990. Additionally, an enzyme-linked immunosorbent assay (ELISA) was also devised and used to identify the antigen involved. Chest X-ray, sinus X-ray and electrocardiogram were performed in all cases and echocardiogram, electromyography or electroneurography was performed when indicated. One or more biopsy specimens from affected tissues were obtained in all cases.

A patient was considered to be in remission when clinical manifestations of CSS, except asthma or neurological sequelae, were not present for at least 6 months.

A relapse was defined as the occurrence of new clinical manifestations of CSS or recurrence of the initial manifestations of the disease, other than asthma, occurring during the time of treatment or the follow-up period.

Follow-up was attempted in all patients to assess both the response to treatment and the morbidity and mortality of the disease. Patients were followed up regularly, initially monthly and later every 2 months, at the internal medicine out-patient clinics. When patients were considered to have been in complete remission for at least 1 yr they were visited every 6 months.

Survival was estimated according to the Kaplan–Meier method using the SPSS statistical package (SPSS, Chicago, IL, USA). The odds ratio [with 95% confidence limits (CI)] was calculated using the Epi Info program (Centers for Disease Control and Prevention, Atlanta, GA, USA, 1995) to assess for associations between categorical variables.

## Results

Between 1977 and 1999, 32 patients (23 women, nine men; mean age 42.5 yr, range 17–85 yr) were diagnosed with CSS in our department. They represented approximately 3% of all patients diagnosed in our department as having vasculitides over the same period. A detailed history was obtained for 24 (75%) patients. A history of allergic rhinitis was noted in 20 (62.5%) patients, with nasal polyposis in eight (25%) cases. Recurrent episodes of paranasal sinusitis were recorded in 12 (37.5%) patients, and were documented on X-rays or computed tomography (CT) scans.

### *Clinical features*

The clinical manifestations of the CSS patients are summarized in Table 1. Asthenia, fever (>38°C) and weight loss (>5% body weight) were common complaints (68.8%) at presentation, but pulmonary and upper respiratory symptoms were the most frequent clinical manifestations at onset of the disease. In effect, asthma was present in all patients and preceded vasculitis development by between 6 months and 29 yr (mean 9 yr) in all patients but one (96.9%), in whom asthma began simultaneously with systemic vasculitis. Asthma was severe and necessitated treatment with oral steroids in 15 patients, 11 of whom had at least one episode of status asthmaticus. One patient experienced alveolar haemorrhage at initial presentation.

Chest X-ray revealed one or more abnormalities in 24 of the 32 (75%) patients. Peripheral transient and patchy alveolar infiltrates were the most frequent radiographic findings. Bronchoalveolar lavage performed in four patients detected alveolar eosinophilia in three and alveolar haemorrhage in one. Thoracentesis performed in four patients yielded in all of them a pleural fluid, which corresponded to an exudate with low glucose and marked eosinophilia.

TABLE 1. Clinical manifestations of Churg–Strauss syndrome

Clinical manifestation	At presentation No. (%)	During follow-up No. (%)	Total No. (%)
Asthma	32 (100%)		32 (100%)
Fever, weight loss	22 (68.8%)	4 (12.5%)	26 (81.3%)
Pulmonary infiltrates	17 (53.1%)	3 (9.4%)	20 (62.5%)
Patchy	15		15
Nodular	1		1
Nodular cavitated	1		1
Bilateral pleural effusion	6 (18.8%)		6 (18.8%)
Alveolar haemorrhage	1 (3.1%)		1 (3.1%)
Skin involvement	22 (68.8%)	4 (12.6%)	26 (81.3%)
Palpable purpura	13	3	16
Maculopapular rash	9	1	10
Digital ischaemic ulcers	3		3
Erythematous nodules	2		2
Raynaud's phenomenon	1 (3.1%)		1 (3.1%)
Mononeuritis multiplex	14 (43.8%)	2 (6.3%)	16 (50%)
Sensorimotor polyneuropathy	7 (21.9%)		7 (21.9%)
CNS involvement	1 (3.1%)	1 (3.1%)	2 (6.2%)
Stroke	1		1
Intracranial haemorrhage		1	1
Horner syndrome	1 (3.1%)		1 (3.1%)
Gastrointestinal involvement	12 (37.5%)	2 (6.2%)	14 (43.8%)
Abdominal pain	7	2	10
Small intestine perforation	2	1	3
Diarrhoea	3	1	4
Cardiac involvement	9 (28.1%)	3 (9.4%)	12 (37.5%)
Myocarditis	1		1
Pericardial effusion	1	2	3
Myopericarditis	3	1	4
Ischaemic cardiomyopathy	4		4
Renal involvement	4 (12.5%)		4 (12.5%)
Glomerulonephritis	1		1
Renal insufficiency	1		1
Haematuria	2		2
Hypertension	5 (15.6%)	2 (6.3%)	7 (25%)
Ophthalmic involvement	2 (6.3%)	3 (9.4%)	5 (15.6%)
Orbital pseudotumour	1	1	2
Sudden blindness	1	2	3
Arthralgia, myalgia	12 (37.5%)	2 (6.3%)	14 (43.8%)

Cutaneous manifestations were present in 26 (81.3%) patients. Recent-onset Raynaud's phenomenon was present in one patient.

Neurological involvement appeared in 26 (81.3%) patients. Sensory impairment was restricted mainly to the lower limbs except in four patients, who developed severe mononeuritis multiplex in the upper limbs and one patient who developed tetraparesis. Muscle weakness was evident in the involved limbs in a distal-dominant fashion. Muscular atrophy became apparent in most patients. All patients responded well to steroid and cyclophosphamide therapy, although some were handicapped and had poor functional long-term outcome. Uncontrollable neuropathic pain was successfully treated in one patient by topical application of capsaicin. Involvement of the central nervous system was observed in two patients. Cranial nerves were intact in all but one patient, who developed transient Horner's syndrome.

Cardiac involvement was present in 12 (37.5%) patients and included acute pericarditis, myocarditis or both, and ischaemic cardiomyopathy. No cardiac tamponade was observed. Pericardiocentesis was performed in two cases and yielded pericardial fluid that

corresponded to an exudate with low glucose and marked eosinophilia. Pericardial biopsy was performed in one patient and showed eosinophilic infiltrates. Four patients suffered ischaemic cardiomyopathy with conduction abnormalities. In addition, three patients suffered isolated cardiac conduction abnormalities that were consistent with rapid atrial fibrillation in two cases and supraventricular paroxysmal tachycardia in one case. Two patients with myocardial involvement presented with rapid-onset left ventricular failure. Two patients developed progressive congestive heart failure and one of them died, although she was treated with high doses of prednisone, cyclophosphamide, digoxin and diuretics. One patient developed severe restrictive cardiomyopathy and was treated with prednisone plus cyclophosphamide. One patient developed myocardial dysfunction and was treated with prednisone plus azathioprine.

Gastrointestinal tract symptoms consistent with abdominal pain, diarrhoea or both were present in 14 (43.8%) patients. Emergency laparotomy was performed in three patients with severe abdominal pain, and revealed perforation of the small intestine with

peritonitis in all cases; two patients died because of this complication. Four patients developed diarrhoea associated with abdominal pain in all cases and with intestinal bleeding in two. Intestinal biopsy was performed in one patient and showed no abnormalities. Three patients had hepatomegaly. Liver biopsy was performed in two patients who showed abnormal liver tests. Necrotizing vasculitis with marked eosinophilia was observed in one case and no abnormalities were found in the remaining patient.

Renal disease was present in four (12.5%) patients at onset of the disease. Renal biopsy was performed in two cases and showed focal segmental glomerulonephritis in one case and necrotizing vasculitis in the other. The first patient improved with prednisone 1.5 mg/kg/day and cyclophosphamide, but the other died. No involvement of the lower urinary tract was observed. Eight (25%) patients developed hypertension.

Ophthalmological manifestations were noted in five (15.6%) cases. Diplopia and unilateral exophthalmos were present in two patients. CT scan of the orbits revealed an inflammatory mass suggestive of an orbital pseudotumour in both cases. A histological specimen obtained from one patient showed necrotizing angiitis, tissue eosinophilia and extravascular granulomas. The pseudotumour appeared during the vasculitic phase in one case and 8 yr after the diagnosis of CSS in the other, while the patient was in remission. Both patients improved rapidly with high doses of steroid (prednisone 1 mg/kg/day). Three patients experienced sudden onset of blindness, one at onset of the disease and the other two during the follow-up period. In two cases amaurosis was presumed to be secondary to underlying vasculitis and treatment with high doses of prednisone was successful. In one case, an acute unilateral amaurosis was due to occlusion of the central artery of the retina, and treatment with prednisone and cyclophosphamide was unsuccessful.

Fourteen patients (43.75%) referred to diffuse myalgia or polyarthralgia during their illness. Five (15.6%) patients developed arthritis involving the knees, elbows, wrist or hands. Arthritis was symmetrical and not erosive, and appeared in the vasculitic phase. Finally, one patient developed myositis with proximal weakness. No muscle biopsy was performed.

#### Laboratory findings

Laboratory findings are presented in Table 2. Leucocytosis with eosinophilia ( $> 1500/\text{mm}^3$  or  $> 10\%$ ) and elevated erythrocyte sedimentation rate (ESR;  $\geq 50$  mm/h) were present in all patients. Absolute eosinophil values ranged from  $0.784 \times 10^9$  to  $31 \times 10^9$  eosinophils/l (mean  $5.55 \times 10^9$  eosinophils/l). The serum concentration of immunoglobulin E (IgE) was increased in 11 of 16 (68.8%) patients tested. ANCA were determined in 26 patients. Eight patients were in complete remission and all were negative for ANCA. Eighteen patients were in the acute phase of the illness and 14 (77.7%) were positive for ANCA by immunofluorescence assay. The staining pattern was perinuclear in 13 cases with

MPO-ANCA by ELISA, and cytoplasmic in one case with anti-PR3 specificity by ELISA. ANCA were also tested during clinical relapses in six patients but were detected in only three cases (50%), with MPO-ANCA specificity by ELISA.

#### Histological findings

The histological findings in CSS patients are shown in Table 3.

All biopsy material available was reviewed. A total of 73 biopsies were performed (17 nerve, 16 muscle, 22 skin, seven lung, four bowel, two liver, one orbital tissue, one pericardium, one pleura and two kidney). Necrotizing vasculitis was found in 47 biopsies, vascular and perivascular eosinophil infiltrates in 40 and extravascular granulomas in 11. Immunofluorescence assay for immunoglobulins or complement was negative in all skin biopsies. Muscle atrophy and denervation was observed in three muscle biopsies. No autopsy was performed.

#### Therapy

Steroid treatment (prednisone 1 mg/kg) was given daily in all patients until a clinical response was evident, and the dose was then tapered progressively. Thirteen (40%) patients were treated with steroids alone. Immunosuppressive agents were used as additional therapy in 19

TABLE 2. Laboratory findings in CSS patients

	No. patients (%)
Eosinophilia $> 1500/\text{mm}^3$ or $> 10\%$	32/32 (100)
ESR $\geq 50$ mm in 1st h	32/32 (100)
Antinuclear antibodies $> 1/160$	3/20 (20)
Rheumatoid factor titre $\geq 40$	5/21 (23.8)
ANCA	14/26 (53.8)
MPO-ANCA	13/26 (50)
c-ANCA	1/26 (3.8)
HBsAg	1/24 (4.2)
Anti-HCV	0/10 (0)

c-ANCA, ANCA with cytoplasmic pattern; HBsAg, hepatitis B surface antigen; anti-HCV, antibodies to hepatitis C virus.

TABLE 3. Histological findings in CSS patients

Biopsy	No.	NVL	TE	EGR	Other	Normal
Skin	22	15	16	5	—	3
Nerve	17	15	12	2	—	2
Muscle	16	4	2	—	2	8
Lung	7	5	4	2	—	1
Bowel	4	3	3	—	—	1
Liver	2	1	—	1	—	1
Kidney	2	1	—	1	1	1
Pleura	1	1	1	—	—	—
Pericardium	1	—	1	—	—	—
Orbital tissue	1	1	1	1	—	—
Total	73	47	40	11	3	17

NVL, necrotizing vasculitis; TE, tissue eosinophilia; EGR, extravascular granulomas.

patients with severe systemic organ involvement (cyclophosphamide in 17 patients and azathioprine in two). Fifteen patients were treated with cyclophosphamide (2 mg/kg/day) orally over a 1–1.5-yr period and two patients with monthly intravenous pulses of cyclophosphamide (0.7 g/m<sup>2</sup>) over a period of 1 yr. Azathioprine was administered at 1.5 mg/kg/day orally in two patients over a 6-month period. One patient who did not respond to initial treatment with prednisone and cyclophosphamide was subsequently treated with azathioprine, intravenous immunoglobulins, interferon- $\alpha$  and plasma exchange, with no improvement. Leucocytosis, eosinophilia and ESR normalized promptly after initiation of treatment.

### Outcome

The clinical outcome was evaluated in all patients. The follow-up period ranged from 4 months to 19 yr. Six (18.7%) patients were lost to follow-up, two of them 2 yr after CSS diagnosis and the remaining four 10 yr after CSS diagnosis; all were in complete remission. Four patients died during follow-up. The remaining 22 patients could be evaluated up to the present time.

Outcome was relatively good in 26 (81.3%) patients, with clinical remission in all after a mean of 14 months of therapy. During follow-up, nine (28.1%) patients suffered 14 clinical relapses after clinical remission. Six relapses occurred early during the first year of therapy and four late (39, 15, 26 and 24 months after CSS diagnosis). For five patients, the clinical manifestations noted at the time of relapse were different from those present at the time of diagnosis. Palpable purpura, pulmonary infiltrate, mononeuritis multiplex, intestinal perforation and arthralgia were the clinical manifestations noted at the time of the relapse. A possible triggering factor for relapse was rapid tapering of steroids in five patients, cocaine smoking in one, a recent influenza vaccination in one, adjunction of montelukast to asthma therapy in one and pregnancy in another. One patient was pregnant during CSS follow-up. She was in complete remission at the time of conception. She suffered several episodes of asthma, rhinitis and purpuric lesions in her lower limbs during pregnancy, which were treated with systemic steroids and a nebulized  $\beta_2$  agonist. No pregnancy-related problems were observed. The fetus was delivered successfully. After delivery, subsequent remission of cutaneous vasculitis was observed with no relapses. The post-partum course was uneventful. Two years later the patient became pregnant again. At 20 weeks of gestation she developed a severe relapse of systemic vasculitis with purpuric lesions in her lower limbs, pulmonary infiltrates and mononeuritis multiplex. Clinical improvement was reached with high doses of steroids and cyclophosphamide but the fetus died in the uterus at 28 weeks of gestation.

Five patients who relapsed responded to an increased dose of prednisone but four patients who experienced more than one relapse required adjunction of other cytotoxic drugs.

One or more adverse side-effects of therapy were observed in 16 (50%) patients during follow-up. Hypercorticism was observed in eight (25%) patients, steroid-induced diabetes mellitus in four (12.5%), steroid-induced myopathy in two (6.3%), osteoporosis with vertebral fractures in two (6.3%), avascular necrosis of the femoral head in one (3.1%), gastrointestinal haemorrhage in three (9.4%) and cyclophosphamide-induced cystitis in one (3.1%). Infectious complications were rarely seen (9.4% of cases) and only one patient developed an opportunistic infection by *Pneumocystis carinii* and cytomegalovirus. One patient developed a colon neoplasm 8 yr after CSS diagnosis, while CSS was in remission.

Four (12.5%) patients died during the follow-up period, and three of the deaths (75%) were directly attributable to vasculitis. Two patients died of an intestinal perforation, 4 and 6 months respectively after CSS diagnosis, although they were treated with prednisone plus cyclophosphamide and prednisone plus azathioprine respectively. One patient died 18 months after CSS diagnosis because of uncontrolled vasculitis with severe cardiac, gastrointestinal and renal involvement, despite treatment with prednisone, cyclophosphamide, azathioprine, immunoglobulins and interferon- $\alpha$ ; plasmapheresis had been attempted. The fourth patient died from nosocomial pneumonia while CSS was in remission, 5 yr after diagnosis.

Survival to 1 yr was achieved by 93.7% (30/32) of patients and survival of 5 yr by 90% (27/30) of patients. Median cumulative survival is now more than 10 yr, and two patients have survived more than 19 yr. The survivorship curve for all patients is shown in Fig. 1.

According to univariate analysis, severe gastrointestinal involvement and severe heart involvement were not statistically associated with a poor outcome

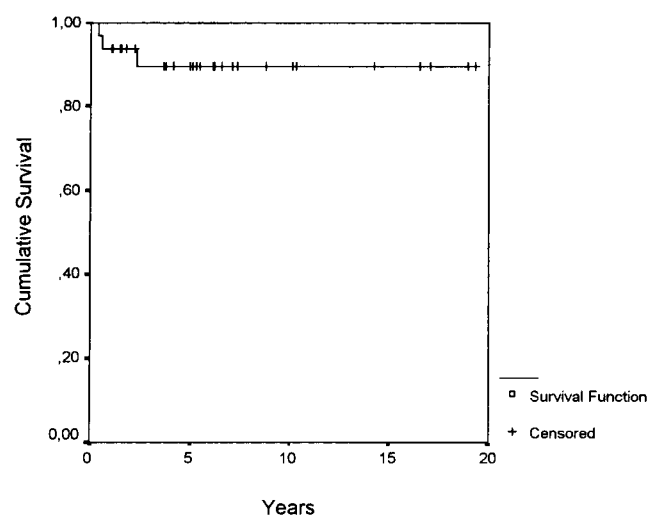


FIG. 1. Cumulative survival estimated according to the Kaplan–Meier method.

[odds ratio 2.83 (95% CI 0.13–176.8) and 0.92 (0.16–4.98) respectively].

Twenty-two patients are currently being monitored in our department and 21 are in complete remission. At the time of the last visit in December 1999 all patients had persistent asthma and seven (31.8%) had required frequent hospital admissions despite permanent treatment with low doses of oral steroids.

Sequelae included hypoaesthesia of the lower limbs, atrophy and weakness with an abnormal gait in six patients, associated with hypoaesthesia of the upper extremities in three cases and neuropathic pain in five. Four patients required prolonged physical rehabilitation to improve their functional status. In addition, cardiac insufficiency persisted in three patients and conduction abnormalities in another three.

## Discussion

Allergic and granulomatous angiitis or CSS is a rare disorder characterized by hypereosinophilia and systemic vasculitis and occurs in patients affected with asthma and allergic rhinitis. Vasculitis commonly affects the lungs, skin, peripheral nerves, heart and gastrointestinal tract [1–3, 6–9]. Renal disease is not a major feature of this disease but does occur. Although not a criterion of CSS diagnosis, the presence of ANCA, especially MPO-ANCA, is frequent in CSS [5, 10]. Here we describe our series of 32 CSS patients, one of the largest series in the literature, with the exception of that recently reported by Guillevin *et al.* [7]. In addition, this is the largest series of CSS patients from a European country collected at a single institution.

A higher number of female than of male patients was observed in our series, in contrast to the predominance of male patients reported by other authors [1–3]; our data are similar to those reported by Guillevin *et al.* [7].

The spectrum of clinical manifestations seen in our patients was similar to that of the largest series published [1–4, 7–9]. Asthma was the most frequently observed manifestation at presentation and in the majority of patients it was exacerbated in the postvasculitic phase.

Skin involvement was present in 81.3% of patients, palpable purpura being the most frequent manifestation. Only one patient developed subcutaneous ulcerated nodules.

Neurological manifestations were present in 75% of patients at presentation of the disease and did not differ from data reported in the literature [1–3, 7, 8, 11]. Mononeuritis multiplex constituted the most frequent manifestation, although sensitive polyneuropathy was present in seven cases. Central nervous system symptoms were exceptional and not related to high mortality in our series, although the small number of observations precludes definitive conclusions. All patients responded well to steroid and cyclophosphamide therapy, although some were handicapped and had poor functional long-term outcome. In one case, uncontrollable neuropathic pain was treated successfully by topical application of capsaicin, the pungent ingredient in chilli peppers which

has selective effects on the functions of sensory neurones and which, if used repeatedly three or four times a day, can limit pain transmission [12]. To our knowledge, no patient treated successfully with this topical drug has been reported.

Cardiac manifestations were observed in 37.5% of patients and included acute pericarditis, myocarditis or both, and ischaemic cardiomyopathy. Arrhythmias were mainly transient and appeared during the vasculitic phase of CSS. Two patients developed progressive congestive heart failure and one severe restrictive cardiomyopathy. We had a good survival rate, in contrast to the fatal outcome reported by several authors [1–3, 7, 13, 14]. In our series, only one patient with refractory congestive heart failure died and long-term survival was good, although cardiac involvement has been reported as a major cause of mortality in CSS patients [14, 15]. Because seven of nine patients with cardiac involvement were treated simultaneously with prednisone and cyclophosphamide because of the involvement of the peripheral nervous system, we speculate that adding immunosuppressive agents, especially cyclophosphamide, to the treatment was effective and improved the prognosis in our patients. In cases reported previously [1–3, 7, 13, 14] treatment has ranged from relatively high doses of prednisone to low doses, combined with digoxin and diuretics, and some patients with myocardial dysfunction or restrictive cardiomyopathy have been treated with prednisone combined with azathioprine [14] or cyclophosphamide [15].

Gastrointestinal tract involvement was common and usually appeared in the vasculitic phase. Abdominal pain was the main manifestation and resulted in three cases from the presence of an intestinal perforation. This complication was the first manifestation of CSS in two cases and was related to a poor prognosis. In contrast, a patient who suffered an intestinal perforation during follow-up was treated successfully with prednisone and azathioprine after surgery. No case of colon involvement was recorded in our series, although multiple mucous ulcers in the colon secondary to local ischaemia have been described in CSS [16]. Long-term survival was good, except for two patients with severe digestive complications, our data being similar to those of the largest series published [1–3, 7, 17].

Renal involvement was rare in our patients, as has been reported previously [1–3, 7, 8–10]. Only one patient developed focal, segmental glomerulonephritis and another necrotizing vasculitis with acute nephritic syndrome. This patient died because of severe renal, cardiac and gastrointestinal involvement refractory to several treatments. Arterial hypertension was frequent in CSS patients, as described recently by Guillevin *et al.* [7].

Arthralgia and myalgia were relatively common in our series, but arthritis was rare.

A high proportion of patients with CSS had pulmonary infiltrates on chest radiographs at the time of diagnosis, as described in the literature [18]. The infiltrates were usually patchy and transient with no preferred location, and showed a cavity in only one

case. In one case, they mimicked chronic eosinophilic pneumonia and in another they corresponded to an alveolar haemorrhage. Standard pulmonary CT was useful in the evaluation of pulmonary disease [19]. The most common CT findings included patchy multifocal peripheral consolidations and bronchial wall thickening. Bronchoalveolar lavage usually showed marked eosinophilia, and transbronchial biopsy, when performed, showed eosinophilic infiltrates and necrotizing vasculitis. We wish to emphasize the usefulness of transbronchial biopsy in diagnosing CSS in our patients with evidence of active pulmonary disease but without gross parenchymal lesions accessible by radiologically guided biopsy, as suggested by Schnabel *et al.* [19]. In addition, because open-lung biopsy is associated with appreciable morbidity while transbronchial biopsy involves fewer risks, we believe the latter should be considered as an alternative diagnostic technique.

Pleural effusions were observed in six patients and the pleural fluid corresponded to an exudate with marked eosinophilia in all cases, as described by Erzurum *et al.* [21]. Pleural biopsy was performed in only one patient and showed eosinophil infiltrates.

Other unusual manifestations were observed. Thus, although ocular involvement is rare in CSS, we observed unilateral exophthalmos due to an orbital pseudotumour in two patients reported previously [22], which resolved with steroid therapy. In addition, two patients suffered sudden amaurosis that was presumed to be secondary to ischaemic optic neuritis due to underlying vasculitis and which resolved with high-dose prednisone, and one patient suffered acute unilateral amaurosis due to occlusion of the central artery of the retina. Despite the rarity of ischaemic optic neuritis, some cases have been reported [23]. In contrast, to our knowledge, involvement of the central artery of the retina has been documented in only one patient, who improved with prednisone and cyclophosphamide [24]. In our case, treatment was unsuccessful. Finally, one patient referred to painful erection with impotentia coeundi that was attributed to pudendum mononeuritis and resolved with steroid and cyclophosphamide therapy. To our knowledge, no patient with this symptom has been reported previously.

Only one patient was pregnant during CSS follow-up in our series. She was in complete remission at the time of both conceptions. The first pregnancy was successful but vasculitis flared severely in the second and the fetus died at 28 weeks of gestation. Vasculitic syndromes rarely occur in association with pregnancy, probably because of the rarity of the disease and its higher incidence around the fifth decade. Pregnancy has been related to a poor fetal prognosis [25], although successful fetal delivery has also been reported [26]. The vasculitic process usually does not involve the placental vessels [25, 26]. However, fetal damage or death can be a result of systemic maternal compromise or of pregnancy termination for maternal indications.

With regard to the pathogenesis of this disease, 68.8% of the patients tested in our series had increased IgE

serum levels and 62.5% had allergic rhinitis (associated with nasal polyposis in 25% of cases) at presentation of the disease. However, no causative agents of CSS were found except for the patient reported previously who smoked cocaine [27]. Two patients had undergone vaccination and two patients had received montelukast (R. Solans *et al.*, unpublished data) before CSS development or relapse. Thus, although it has been suggested that immediate hypersensitivity could play a role in the pathogenesis of CSS owing to the presence of tissue and peripheral eosinophilia, bronchial asthma and an increase in the plasma IgE level [3, 8] no data supporting this theory were obtained in our series.

Finally, 77.8% of tested patients were positive for ANCA in the acute phase of the disease, our results being similar to those reported previously [5, 7–9]. However, ANCA were not useful for the monitoring of disease activity as only 50% of patients were positive during clinical relapses. Thus, ANCA were a valuable adjunct supporting the diagnosis of CSS in our series but histological confirmation remained a mainstay of diagnosis. Laboratory variables best indicating the response to treatment and disease activity were the eosinophil count, total white count and ESR.

In our series 40.6% of patients were treated with steroids alone for a period of 12–18 months with good outcome. Immunosuppressive agents were added to the treatment in patients with severe neurological, cardiac or gastrointestinal involvement. Oral cyclophosphamide (2 mg/kg/day) was the most frequently used treatment. Monthly intravenous cyclophosphamide pulses were administered to only two patients, once a month for 12 months, with no differences in clinical outcome and follow-up, although the small number of patients treated precludes any conclusions. Previous reports have suggested that intermittent high-dose intravenous cyclophosphamide is efficacious for a shorter time than oral therapy [28, 29]. Combined prednisone–azathioprine therapy was administered successfully in two patients, one with severe cardiac involvement and the other with severe gastrointestinal involvement, both patients achieving prolonged remission of CSS [30]. Plasma exchange was used in one patient with severe vasculitis and multisystem failure and gave no improvement, although the procedure appears to be useful in the initial control of the disease [31]. In this patient intravenous immunoglobulins and interferon- $\alpha$  were also tried, with no improvement in the disease, although some reports have suggested their usefulness in treating patients with CSS who had been resistant to steroids [32, 33].

Severe treatment-related adverse effects were relatively uncommon in our series. Metabolic complications appeared late during follow-up and were more frequent in patients who required permanent low doses of steroids to control asthma. Only one patient developed a severe opportunistic infection with *Pneumocystis carinii* and cytomegalovirus.

Outcome was relatively good in our patients, with few clinical relapses after the first year of therapy. Three

patients died directly from vasculitis because of severe gastrointestinal involvement, isolated or associated with renal and cardiac involvement. The mean duration of asthma before the onset of vasculitis did not differ between patients who died and those who remained alive. The most frequent sequelae were dysaesthesiae, atrophy and weakness of the distal limbs, neuropathic pain and cardiac insufficiency.

In summary, we conclude that CSS is an easily recognizable entity, distinct from microscopic and classical polyangiitis, although these conditions have similar extrapulmonary manifestations. The lung is the most common organ involved, followed by the skin and nervous system. Extravascular granulomas are rarely seen in biopsy specimens and thus their absence did not permit the diagnosis of CSS to be ruled out. ANCA, specifically MPO-ANCA, are a valuable adjunct in supporting the diagnosis of CSS but are not useful for monitoring disease activity. The outcome and long-term survival of CSS patients treated with steroids alone or in combination with immunosuppressive agents are good, although steroid-dependent asthma is a frequent condition in CSS. Clinical relapses are rare after the first year of therapy. CSS has a low mortality rate compared with other systemic vasculitides.

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