

Clinical and laboratory characteristics of nineteen patients with Churg-Strauss syndrome from a single South Australian centre

ABSTRACT:

Background: Churg-Strauss syndrome (CSS) is a rare, idiopathic systemic vasculitis. There is emerging evidence of an association between presence or absence of antineutrophil cytoplasmic antibodies (ANCA) and clinical phenotype. Thromboembolism is an increasingly recognised complication of the disease.

Aims: Given the paucity of Australian data, the aim of this study was to examine the clinical and laboratory features of CSS in a single Australian centre.

Methods: We performed a retrospective review of all patients who fulfilled the American College of Rheumatology classification criteria for CSS managed at the Department of Immunology, Royal Adelaide Hospital between 2002 and 2008.

Results: Nineteen patients were included. All patients had asthma and most had upper airway involvement. Peripheral nerve, musculoskeletal, gastrointestinal and cutaneous involvement was common. Renal and cardiac involvement was uncommon in this series. Histological confirmation was obtained in 15 patients (78.9%). Ten patients (52.6%) were ANCA+, and these were more likely to have musculoskeletal involvement such as arthralgia or myalgia (OR 57, p 0.005). Thrombosis was a feature at diagnosis in 6 patients (31.6%); two of these recurred with relapse. Sixteen patients (84.2%) were followed up; five died, and mean survival was 8.9 years.

Conclusions: This is the first Australian study to focus on CSS. Our results demonstrate similar presentation and prognosis of CSS to previous descriptions, however we noted that musculoskeletal involvement was more common in ANCA+ patients. In our series thrombosis was a significant complication and we suggest that thromboprophylaxis may be warranted.

KEYWORDS:

Churg-Strauss syndrome, vasculitis, antineutrophil cytoplasmic antibodies, thrombosis, epidemiology

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BACKGROUND:

Churg-Strauss syndrome (CSS) is a rare systemic necrotising granulomatous vasculitis predominantly affecting small blood vessels. Eosinophilic rhinosinusitis and asthma generally precede the diagnosis of CSS by many years. Characteristically, eosinophilia is found in the peripheral blood and tissues, particularly the lung and gastrointestinal tract¹. Systemic necrotising vasculitis may develop years

later and affect almost any organ including the skin, peripheral nerves, kidneys, heart, muscles and joints, and central nervous system.

Patients may be divided into those with antineutrophil cytoplasmic antibodies (ANCA+) and those without (ANCA-). When present, ANCA usually give a perinuclear staining pattern (pANCA) by indirect immunofluorescence and myeloperoxidase (MPO) specificity by enzyme-linked immunosorbent assay. Retrospective analyses have suggested that ANCA+ patients have lower mortality, higher relapse rates, more frequent renal and peripheral nerve involvement and less cardiac involvement than ANCA- patients^{2,3,4}. Factors associated with poor prognosis include significant proteinuria, elevated serum creatinine, cardiomyopathy, gastrointestinal tract involvement and central nervous system involvement. These have led to the proposed five factor score (FFS) at diagnosis; patients are stratified as “poor prognosis” when the FFS >1⁵. However, 5-year survival exceeds 90%⁶.

Thrombosis is an increasingly recognised feature of ANCA-associated vasculitis (AAV)⁷. Evidence has been mostly restricted to AAV other than CSS, although case series of CSS have identified arterial or venous thromboembolic disease in up to 30% of patients⁸. The risk of thrombosis appears to be greatest during periods of active vasculitis, although this has not been confirmed by prospective studies.

To date, no study has examined the clinical and laboratory characteristics of CSS in Australia. One epidemiological study of primary systemic vasculitis included patients with CSS, although clinical features were not described. The study found annual incidence of 2.2-2.3 per million persons per year, which is comparable to similar populations⁹. The same study found that the prevalence of CSS in the general population in 1995-1999 was 9 per million persons, rising to 18 per million in 2000-2004.

Given the paucity of Australian data, we aimed to describe the clinical and laboratory features, complications, and prognosis of patients with CSS at a single Australian centre. Our results showed a similar presentation and prognosis to previous descriptions, however we noted that musculoskeletal involvement was more common in ANCA+ patients, and thromboembolic disease was a significant complication.

PATIENTS AND METHODS:

This was a retrospective review of records of all patients with CSS managed through the Immunology Department at the Royal Adelaide Hospital between 2002 and 2008. After identification of potential cases by senior clinicians, pre-defined data were extracted from the medical records and tabulated by a medical officer (SNS), and data were validated by a second medical officer (AFW). Cases were excluded from the final analysis if they failed to meet at least four of the six American College of Rheumatology (ACR) classification criteria¹⁰. Data were de-identified after collection. The study was approved by the Royal Adelaide Hospital Research Ethics Committee.

Patient characteristics are reported as number and percentage for categorical variables, and as mean and range for continuous variables. Differences in proportions between groups were tested using the Fisher's exact test and expressed as an odds ratio (OR) with 95% confidence intervals (95% CI). A two-sided p value of 0.05 was considered significant, and no adjustment was used for multiple statistical testing. Patient survival was calculated as time between diagnosis and death (complete responses) or diagnosis and last follow up (censored responses). Where data were missing, the patient was excluded from analysis of that variable.

Statistical analysis was performed using GraphPad Prism software version 5 (PRISM5) (GraphPad Software, Inc, La Jolla, California, USA).

RESULTS:

Nineteen patients achieved a diagnosis of CSS: 10 males and 9 females. One patient with a clinical consensus diagnosis of CSS met only 3 ACR criteria and was excluded. Mean age at onset was 54 years (range 29-75), and mean follow up was 6.0 years (range 0-21). Five patients (26.3%) died. Montelukast was used before onset in one patient (5.3%) and during stable remission in another.

At diagnosis, all patients had a history of asthma and 17 (89.5%) had rhinosinusitis and/or polyposis. Twelve patients (63.2%) had peripheral nerve involvement; 9 (47.4%) had mononeuritis multiplex (3 of whom had cranial nerve involvement), and 3 had mononeuropathy. Eight patients (42.1%) had gastrointestinal symptoms, including gastro-oesophageal reflux, diarrhoea, abdominal pain, and rectal bleeding. Seven patients (36.8%) had rashes: 5 had palpable purpura, one had morbilliform rash, and one was not described. Ten patients (52.6%) had musculoskeletal symptoms, including 5 with migratory polyarthralgia, 4 with myalgia, and 1 with both. Three patients (10.5%) had renal, and two (5.3%) had cardiac involvement. Table 1 summarises these data.

Upper airway involvement occurred at a mean age of 40.4 years (range 29-64). Asthma began at age 40.8 years (range 2-73), preceding vasculitis by an average of 13.2 years (range 0-46). Seven patients (36.8%) had a prodrome of constitutional features prior to the diagnosis of vasculitis.

Mean eosinophilia at diagnosis was 9,790/mm³ (range 750-45,900; reference range (RR) <500), C-reactive protein (CRP) was 81mg/L (range 4-200; RR <8) and erythrocyte sedimentation rate (ESR) was 42mm (range 4-100; RR <20). Mean creatinine was 85.5mmol/L (range 40-182, RR <100).

Sixteen patients (84.2%) had up to three biopsies. Histological confirmation of vasculitis was obtained from skin (5 patients), muscle (5 patients), lung (3 patients), gastrointestinal tract (2 patients, including one with eosinophilic appendicitis), kidney (2 patients), and peripheral nerve (one patient).

Eight patients (42.1%) were pANCA/MPO+, one (5.3%) was cytoplasmic ANCA (cANCA)/proteinase 3 (PR3)+, one (5.3%) was cANCA/MPO+/PR3+, and 4 (21.1%) were ANCA negative; 5 results were not available. Nine of 12 patients (75%) with peripheral nerve involvement, one of 2 (50%) with cardiac involvement, and all three patients with renal involvement, were ANCA+. Of 5 deaths, three were ANCA+; the result was not available for the remaining two. ANCA+ patients were more likely to have musculoskeletal involvement (OR 57; 95% CI 1.9-1695; p 0.005), but there were no other significant differences (Table 2). FFS was 0 in 8 patients (42.1%), and >1 in 11 (57.9%). There was no association between FFS and requirement for additional immunosuppression or mortality.

Thrombosis was a feature at diagnosis in 6 patients (31.6%); 2 patients had pulmonary embolism (PE), one had thrombosis of subclavian, internal jugular and external jugular veins, one had an internal capsule ischaemic stroke, one had internal jugular and lower limb deep vein thrombosis (DVT), and one had lower limb DVT only. Furthermore, the last 2 had recurrence of DVT with relapse of vasculitis. One patient had a past history of DVT. Of the 6 patients, 5 had anticardiolipin antibodies measured, with or without lupus anticoagulant, protein C, protein S, antithrombin III, prothrombin gene mutation, and Factor V Leiden. No abnormalities were detected.

All patients received induction treatment with prednisolone. Methylprednisolone was used in one case and cyclophosphamide in 4 cases. Twelve patients (63.2%) relapsed; all received prednisolone. Additional immunosuppression for relapses was cyclophosphamide (3 cases), intravenous immunoglobulin (2 cases), and methylprednisolone (1 case). Six patients were documented as (31.6%) receiving maintenance prednisolone; 4 of these and 2 others received methotrexate or azathioprine. Complications of treatment were documented in 9 cases (47.4%) and included infections, osteoporosis, persistent neuropathy, and metastatic skin malignancy.

Follow-up data were available for 16 patients (84.2%). Of these, 12 (75.0%) relapsed, and mean time to first relapse was 21.7 months (range 3-69) (Figure 1a). Patients had an average of 2.19 relapses (range 0-6). During relapse, mean eosinophilia was 6,606/mm³ (range 300-25,300), CRP was 88.7mg/L (range 4-130), and ESR was 42mm (range 10-104). Patients were followed for a mean of 6.0 years (range 0-21), and mean survival was 8.9 years (range 5.7-11.4) (Figure 1b).

Of 5 patients who died, one died suddenly on a background of a long history of unstable coronary vascular disease, and two died of metastatic squamous cell carcinoma (SCC) of the skin. Of those with metastatic SCC, one had received cyclophosphamide induction therapy, and both received prednisolone. The cause of death in the remaining two cases was not available.

DISCUSSION:

This is the first Australian study to specifically examine CSS. Its objective was to characterise the clinical and laboratory features of patients with CSS from a single centre. We achieved this by retrospective analysis of case records. The cardinal clinical and laboratory features of our cases are consistent with previous case series. However, while our findings fail to support recent description of ANCA-defined subgroups, they contribute substantially to the growing recognition of thrombosis as a complication of CSS.

Our results support the classical clinical progression of CSS from a prodromal phase of asthma, rhinosinusitis, and nasal polyposis to overt granulomatous vasculitis¹. The delay between onset of asthma and vasculitis is highly variable (2 months to 30 years), but usually averages 3-4 years^{6,11}. We found a slightly longer mean interval, although the range in our study (0-46 years) was comparable to previous data.

The vasculitic manifestations of CSS can involve almost any organ, but the most common are the lungs, peripheral nerves, kidneys, skin, and gastrointestinal tract. The rates of peripheral nerve, lung, skin and gastrointestinal involvement in our study are comparable to previous studies^{1,3,6,12,13,14}. However, the rate of cardiac and renal involvement in our study is lower than previously described^{2,3,6,11,12,15}. This may reflect selection bias from inclusion of patients managed primarily through the Immunology department, although there may also be earlier recognition of disease, or under-recognition of cardiac involvement given recent evidence suggesting that subclinical cardiac involvement may persist despite apparent remission¹⁶.

Three studies have suggested that ANCA- patients have a greater likelihood of cardiac and gastrointestinal involvement, pulmonary infiltrates, and fevers/sweats compared with anti-MPO positive patients, who in turn have more renal involvement^{2,3,4}. All patients in this series with renal involvement, and the majority with peripheral nerve involvement were ANCA+. This is consistent with recent data², and the failure to reach statistical significance in our study likely represents lack of power due to the small sample size. As with a previous study which found a non-statistically significant trend⁴, our data suggests greater musculoskeletal involvement in ANCA+ patients. Features included migratory polyarthralgia in 6 patients and myalgia in 5 patients. Four patients with myalgia had muscle biopsies, and all showed vasculitis with eosinophilic infiltrate. In addition, one patient with no documented musculoskeletal symptoms had eosinophilic vasculitis on muscle biopsy; ANCA result at diagnosis was not available for this patient. While intriguing, this finding is not conclusive and requires further study.

The risk of thromboembolic disease in AAV has been recognised for some years^{7,17,18,19}, and evidence has emerged more recently of a similar risk in CSS²⁰. Although first noted in 1986²¹, more recently^{22,23}, a meta-analysis of retrospective case series supported this association, finding arterial and venous thromboembolic disease in 3.1%-30% of cases⁸. The present study not only confirms the association, but has the highest rate of thrombosis in CSS hitherto reported (31.6%). Furthermore, except for one patient with a past history of DVT, all thrombotic episodes occurred at diagnosis or during relapse and no patient had an underlying hypercoagulable state, suggesting primary and secondary thromboprophylaxis should be considered during periods of vasculitis activity.

Current recommendations are that corticosteroids and additional immunosuppression be used for both remission induction and maintenance therapy²⁴, but few of our patients received additional induction therapy with methotrexate or cyclophosphamide. While corticosteroids alone can achieve remission in the majority of cases without poor prognostic features²⁵, more patients relapsed in this study than in other studies^{6,12}. Fewer than half our patients received maintenance immunosuppression, which again may account for the higher relapse rate, as current recommendations are that all patients receive long-term immunosuppression²⁴. Most patients relapsed within 18 months and survival was comparable to other series^{2,3,15}. Our findings do not support the prognostic stratification of patients based on the FFS, although this may be related to sample size.

This study was limited not only by its retrospective nature with consequent reliance on accurate case records, but also by the exclusion of patients who failed to meet at least 4 of the 6 ACR criteria. While this resulted in exclusion of one patient with a clinical diagnosis of CSS, we used the ACR

criteria because of their specificity of 99.7% in differentiating CSS from other primary vasculitides¹⁰.

The study was small, which limits the conclusions that can be drawn.

CONCLUSION:

This study provides clinical and laboratory correlation regarding CSS in Australia. We have demonstrated that while most of the clinical and laboratory features in our population are consistent with those described elsewhere, there were some notable observations. Firstly, we found a dramatic and statistically significant association between ANCA positivity and musculoskeletal involvement such as arthralgia or myalgia. Secondly, in comparison with other reported cohorts, our patients responded more often to prednisolone alone, although more recent recommendations are that all patients receive methotrexate or cyclophosphamide. Possibly because of this, our patients had a higher rate of relapse, although survival was comparable to other studies. Finally, our results confirm the increasingly recognised association of thrombosis with CSS.

Larger studies, likely including multiple sites, will be needed to further assess the association of musculoskeletal symptoms with ANCA. We suggest that the high incidence of thrombosis in patients with active CSS may justify thromboprophylaxis, but this should be subject to prospective investigation.

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TABLE 1: Clinical organ involvement and laboratory characteristics of this series of 19 patients with Churg-Strauss syndrome

Patient	Sex	Age at onset (years)	Asthma	Upper airway	Renal	Skin	Peripheral nerves	Central nervous system	Gastro-intestinal	Musculo-skeletal	Cardiac	Thromb-osis	ANCA ^a	Biopsy ^b	Time to relapse (months)	Total relapses	Follow-up (years)	Age at death (years)
1	M	44	+	+	+	+	+		+	+			P	R	6	6	11	
2	F	36	+	+											8	6	21	
3	M	75	+	+			+		+	+			P		2	5	9	83
4	F	47	+	+			+		+			+	N	G	16	3	9	
5	F	72	+	+		+	+			+			P	S,M,N	14	3	4	83
6	M	40	+	+	+	+			+	+	+		P	R	47	1	9	
7	M	65	+	+	+		+		+	+			P	S,M		0	1	
8	M	63	+	+			+		+	+			P	M	4	1	0.5	
9	F	57	+	+		+	+		+	+			C			0	3	
10	F	51	+	+			+	+		+		+	P	M			0	
11	F	46	+	+		+	+				+		N	S			0	
12	M	47	+	+					+			+		G	69	1	6	
13	M	63	+							+		+		L	3	2	2	68
14	F	68	+				+						P	S			0	
15	M	58	+	+										L	16	4	6	
16	M	59	+			+	+			(+) ^c		+		M,N		0	11	69
17	M	69	+	+			+	+		+		+	C	L		0	8	76

18	F	29	+	+	+			N	S	47	1	5	
19	F	38	+	+			+	N		28	2	9	

^aAntineutrophil cytoplasmic antibodies: P=perinuclear immunofluorescence pattern, C=cytoplasmic immunofluorescence pattern, N=negative

^bR=renal, G=gastrointestinal tract, S=skin, M=muscle, N=nerve, L=lung

^cAsymptomatic eosinophilic vasculitis

TABLE 2: Comparison of specific organ involvement between ANCA positive and ANCA negative patients

	ANCA unknown (%), n=5	ANCA positive (%), n=10	ANCA negative (%), n=4	Odds Ratio (95% confidence interval)	p value
Renal	0 (0)	3 (30)	0 (0)	4.2 (0.2 to 101.6)	0.51
Cutaneous	1 (20)	4 (40)	2 (50)	0.7 (0.1 to 6.0)	1.00
Peripheral neuropathy	1 (20)	9 (90)	2 (50)	9.0 (0.5 to 155.4)	0.18
Central nervous system	0 (0)	2 (20)	0 (0)	2.6 (0.1 to 67.9)	1.00
Gastrointestinal	1 (20)	6 (60)	1 (25)	4.5 (0.3 to 60.2)	0.56
Musculoskeletal	1 (20)	9 (90)	0 (0)	57.0 (1.9 to 1695.0)	0.005
Cardiac	0 (0)	1 (10)	1 (25)	0.3 (0.02 to 7.1)	0.51
Thrombosis	3 (60)	1 (10)	1 (25)	0.3 (0.02 to 3.0)	0.52

FIGURE 1: Kaplan-Meier analysis curve showing (a) the time to first relapse in 16 patients followed up in this series of Churg-Strauss syndrome patients, and (b) overall survival. A drop in the line indicates a relapse/death, while a tick mark indicates censored data (patient alive at end of follow up).

