Clinical and pathological features of Churg Strauss syndrome among a Japanese population: a case series of 18 patients

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Summary

Background: **Many autoimmune diseases differ in individual of different races, but there has been very scarce information on the clinicopathological features of Churg Strauss syndrome (CSS) among Asians patients.**

Objective: **To clarify the clinicopathological details of Japanese CSS patients.**

Methods: **The medical records of CSS patients hospitalized in l980-2007 were carefully reviewed.**

Results: **Seventeen patients fulfilled the Japanese Ministry of Health, Labour and Welfare (MHLW) criteria and all 18 fulfilled the American College of Rheumatology criteria. Sixteen patients (89%) had the history of asthma. Frequently involved organs were peripheral nerves (PNS) (94%), skin (50%), gastrointestinal tract (33%), kidney (22%), and heart (17%). The mean (range) eosinophil count, C-reactive protein, and number of damaged organs was 18,108 (3,820-36,760)/μL, 51 (0-126) mg/L, and 2.7 (1-6), respectively. Four patients died, of whom three had heart involvement while only one without it died (100 versus 9%, respectively, *p* =0.0088).**

Regarding the pathology, vasculitis was observed in six of seven skin but in only 2 of 10 PNS biopsies. Eosinophilia was found in all of the tissues except for PNS and muscle (40%). Granuloma was observed in only three of the total of 29 biopsies.

Conclusion: **The usefulness of MHLW criteria was verified. The clinical features of Japanese CSS patients were mostly similar to those previously reported, except for lower asthma- and ANCA-positivity rates. Regarding the pathology, vasculitis and eosinophilia were much more frequently observed in skin.** ***(Asian Pac J Allergy Immunol 2012;30:61-70)***

Key words: *Churg Strauss syndrome, outcomes, glucocorticoids, antineutrophil cytoplasmic antibodies, Asian continental ancestry group, clinical pathology*

AAV	=	ANCA-associated vasculitis
ACR	=	American College of Rheumatology
ANCA	=	Antineutrophil cytoplasmic antibodies
CHCC	=	Chapel Hill Consensus Criteria
CNS	=	Central nervous system
CSS	=	Churg Strauss syndrome
CYC	=	Cyclophosphamide
FFS	=	Five-factors score
GI	=	Gastrointestinal
LTRA	=	Leukotriene receptor antagonist
MHLW	=	Ministry of Health, Labour and Welfare
PNS	=	Peripheral nerve system

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Introduction

Churg and Strauss reported 13 patients with severe bronchial asthma and disseminated necrotizing vasculitis in 1951 and the syndrome was named allergic granulomatosis and angiitis, or Churg Strauss syndrome (CSS).[1] It is a very rare vasculitis syndrome seen exclusively among those with asthma, allergic rhinitis, or sinusitis and is

characterized by systemic small to medium-sized vessel necrotizing vasculitis, vascular or extravascular granulomas often containing abundant eosinophils, eosinophilia, and eosinophilic tissue infiltration.[1,2,3]

Although not applicable to all cases, CSS is known to exhibit a typical phase pattern.[1,3,4,5] First, asthma usually occurs long before the onset of CSS, and allergic rhinitis, sinusitis, and nasal polyps often precede asthma; the next phase is marked by eosinophilia in the blood or in tissues; and the third phase is vasculitis, which involves the skin, lungs, nerves, kidneys, and other organs. A characteristic feature is that antineutrophil cytoplasmic antibodies (ANCA), especially myeloperoxidase (MPO)-ANCA, are frequently found among patients with CSS (35-78%).[6-9] Recently, CSS is often included in ANCA-associated vasculitis together with Wegener's granulomatosis and microscopic poly-angiitis, although it has many unique features, as noted above.[3,6,7,10,11]

At present, several different diagnostic criteria for CSS are used, partly due to its rarity.[3] The American College of Rheumatology (ACR) criteria[12] are generally accepted as standard. ACR criteria include six items: asthma, eosinophilia ＞10% of the white blood cell count, mononeuropathy or polyneuropathy, non-fixed pulmonary infiltrate on chest X-ray, paranasal sinus abnormality, and a pathological specimen containing extravascular eosinophil infiltration, and one who has four or more of these six items is diagnosed with CSS.

The Chapel Hill Consensus Criteria (CHCC) put emphasis on pathological findings, defining CSS as a necrotizing vasculitis affecting small-to-medium-sized vessels with eosinophil-rich granulomatous inflammation involving the respiratory tract, accompanied by asthma and eosinophilia.[13]

In Japan, the criteria proposed by the Ministry of Health, Labour and Welfare of Japan are often used. They require the presence of three major clinical items: 1) asthma or allergic rhinitis, 2) eosinophilia, 3) and the presence of clinical vasculitis.[14] In this context, we call them MHLW criteria.

CSS is made up of various stages and it is generally accepted that vasculitis affects vessels in a skipped and segmental pattern and biopsied specimens do not always include positive findings even when the clinical symptoms strongly suggest the presence of vasculitis.[2] The recent ACR criteria do not require strict pathological evidence for CSS and have made the diagnosis rapid and convenient. The advantage of this simplification may be that the risk of delayed diagnosis and irreversible morbidity could be reduced. However, simplification of the diagnosis risks the over diagnosis of CSS in patients with milder eosinophilic diseases and so excessive immunosuppressive treatment is a matter of concern. From this point of view, we think that it is important to reassess pathological features and re-evaluate the significance, benefits, and demerits of biopsy.

It is known that autoimmune diseases differ among races in many aspects of clinical features and the difference is regarded as being influenced by environmental and genetic factors.[15,16] As for ANCA-associated vasculitis (AAV), a marked difference is seen in the characteristics between the West and Japan: PR3-ANCA-positivity and Wegener's granulomatosis are common among AAV in the West, but they are rare and microscopic polyangiitis with MPO-ANCA comprises most of AAV in Japan.[17] Likewise, the features of CSS may largely vary dependent on races, but all the case series of CSS except for one small series from Korea[18] are from the West.[5,6,8,9,19-22] Interestingly, angioedema associated with eosinophilia, a clinical entity which belongs to diseases related to eosinophilia, as with CSS, has been known to differ greatly dependent on the region.[23] Under these circumstances, we think that it is important to gather more cases from our region and we hope to help advance understanding of this rare disease and also clarify features characteristic of Japanese populations through this article.

Methods

The medical records of CSS patients who required hospitalization in Tokyo Metropolitan Komagome Hospital between January 1980 and December 2007 were carefully reviewed retrospectively, and essential clinical data were extracted. The items investigated were:

1. Patient background (sex, presence of atopic airway disease and its details, duration of asthma, previous use of LTRA)
2. Laboratory findings **(**white blood cell count (including eosinophils), chemistry (liver function, renal function), immunoglobulin E (IgE), C-reactive protein (CRP), rheumatoid factor (RF), MPO-ANCA, urinary test, urinary sediment test)
3. Survival outcome

Table 1. The clinical background of CSS patients

Age (years, mean (range))	59 (39-76)
Sex (male: female)	8:10
Previous use of LTRA (n)	3 (17%)
Duration of asthma (years, mean (range))	6.1 (1-24)
Asthma (n)	16 (89%)
Atopic airway disease (n)	17 (94%)

4. Use of glucocorticoid, pulsed methylprednisolone, and immunosuppressants
5. Organ involvement
6. Pathological and autopsy findings

As for patient background, the relationship between leukotriene receptor antagonist (LTRA) use and the occurrence of CSS was investigated by retrospectively surveying 3,253 patients with asthma who had been seen in our hospital between 1998 and 2004. Regarding the survival prognosis, only patients who continued to attend our hospital until the end of the research period were subjected to analysis.

As for organ involvement, the following were investigated: central nervous system (CNS), peripheral nervous system (PNS), lung, heart, kidney, gastrointestinal (GI) tract, skin, muscles. Peripheral neurological involvement was diagnosed when newly developed mononeuropathy or multiple mononeuropathies, which coincided with the occurrence of eosinophilia or other systemic symptoms, were present. Cardiac involvement was diagnosed by impaired wall motion or worsening cardiomegaly that was known to have developed within the six months prior to the diagnosis. The involvement of muscles was diagnosed only when specialized neurologists judged that it was not caused secondarily by PNS damage. The kidney was regarded as being involved if a patient had proteinuria ≥ 0.5 g/day or ≥ 2+ protein and ≥ 2+ occult blood on urine dipstick, or the patient's serum creatinine increased by ≥ 30%. Lung involvement was diagnosed when the patients showed non-fixed lung infiltration suggestive of eosinophilic pneumonia or eosinophilic and aseptic pleural effusion.

Figure 1

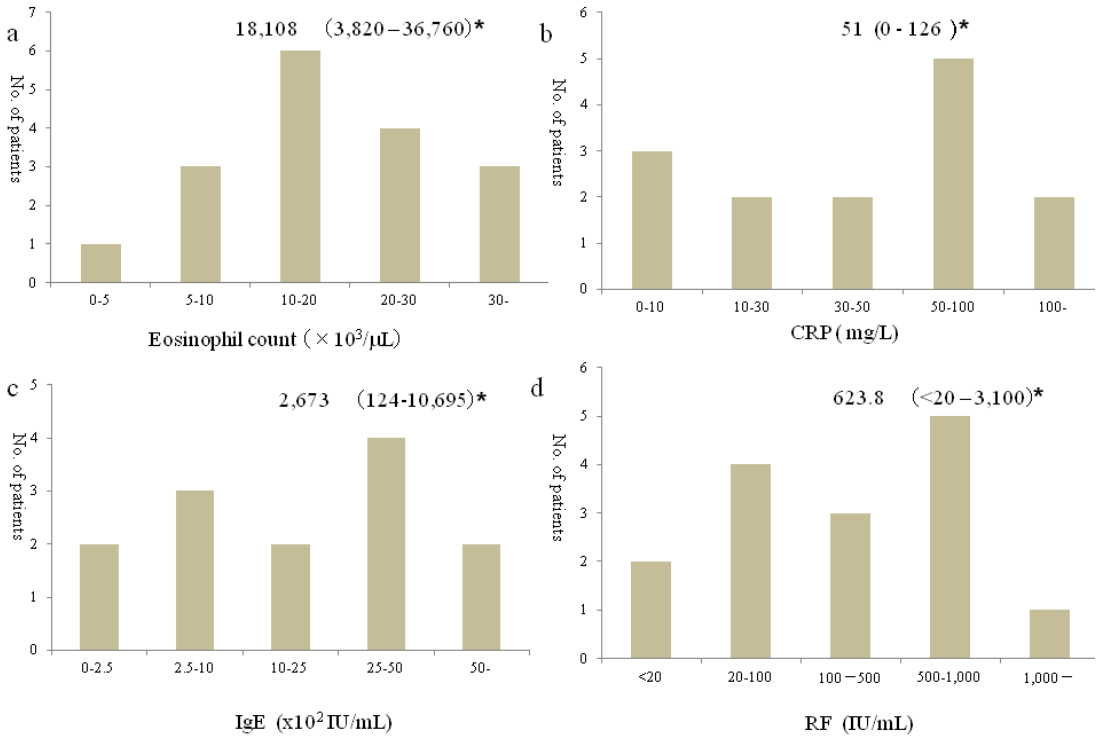

Figure 1. Distributions of the eosinophil count (a), CRP (b), serum IgE level (c), and RF (d) among CSS patients. The mean (range) of each parameter is shown in the upper right corner of each figure (designated by *).

Table 2. Factors included in the Ministry of Health, Labour and Welfare (MHLW) and American College of Rheumatology (ACR) criteria, the positivity of each factor, and fulfilment of the diagnostic criteria among CSS patients.

	ACR (≥4 of 6 factors)							Diagnosis	
	MHLW (≥3 of 4 factors, with mandatory inclusion of the first two factors)								
Case	clinical vasculitis	blood eosinophilia	asthma	nasal symptoms	neuoropathy	lung shadow	tissue eosinophilia	MHLW	ACR
1	+	+	+	+	+		+	+	+
2	+	+	+		+		+	+	+
3	+	+	+	+	+			+	+
4	+	+			+	+	+		+
5	+	+	+	+	+			+	+
6	+	+	+	+	+			+	+
7	+	+	+	+	+	+		+	+
8	+	+	+	+	+			+	+
9	+	+	+		+		+	+	+
10	+	+	+	+	+		+	+	+
11	+	+	+	+			+	+	+
12	+	+	+		+		+	+	+
13	+	+	+		+	+	+	+	+
14	+	+	+	+	+		+	+	+
15	+	+	+		+	+	+	+	+
16	+	+		+	+		+	+	+
17	+	+	+	+	+			+	+
18	+	+	+		+			+	+

The MHLW and ACR criteria contain four and six factors shown under the lines, respectively.

This study was ethically approved by local ethical committee, in compliance with the Declaration of Helsinki.

Statistical analysis

The statistical relationship between each clinical parameter was analyzed employing either of the following methods depending on the character of each variable: Student's t-test, Fischer's exact test, Pearson's correlation coefficient (designated as r). The results were considered to be significant if the *p*-value was not more than 0.05.

To analyze the correlation between each organ's involvement and the total number of damaged organs, the organ to be investigated was deducted from the total number and the relationship between them was calculated.

Results

The clinical background of CSS patients and evidence for the diagnosis

Eighteen patients were diagnosed with CSS during the research period and 17 (94%) had had preceding atopic airway disease. Sixteen (89%) had a preceding history of asthma and its duration before diagnosis was 6.1 (1-24) years (mean (range)). One patient was not suffering from asthma but had a preceding history of allergic rhinitis and sinusitis. LTRA was used for three patients (pranlukast for one, montelukast for two), and the duration of its use was 1.5, 2.3, and 4.2 years. The precise characteristics of the patients are shown in Table 1.

Table 3. The detailed clinical characteristics of 18 CSS patients

Patient	Damaged organs								Eosinophils	CRP	MPO-ANCA	LTRA	Survival**
No.	CNS	PNS	Heart	Lung	GI	Kidney	Skin	Muscles	($x10^3/\mu L$)	(mg/L)			
1	+	+					+		36.8	36	-	+	0
2		+				+		+	13	87	+	-	N.A.
3		+					+		5.2	N.A.	-	-	0
4		+	+	+	+	+	+		14.9	97	-	-	1
5		+							21.6	N.A.	N.A.	N.A.	N.A.
6		+							9.6	N.A.	+	-	0
7	+	+	+	+	+				30.8	N.A.	N.A.	-	1
8		+						+	3.8	1	-	+	0
9		+		+			+		20.2	75	-	-	0
10		+			+			+	11.3	0	N.A.	-	0
11							+	+	17.4	22	-	-	1
12		+				+	+		8.1	11	+	-	0
13		+		+					15.3	106	-	+	0
14		+			+		+		N.A.*	30	N.A.	-	N.A.
15		+	+	+					24.4	50	N.A.	-	1
16		+			+		+		31.3	126	-	-	0
17		+			+	+			18.2	57	+	-	0
18		+					+		26.1	4	-	-	0

* not available, ** 0= survival, 1= death

As far as the diagnostic criteria are concerned, 18 (100%) fulfilled the ACR criteria, and seventeen (94%) fulfilled the MHLW criteria, as shown in Table 2. One patient (Case 4) did not fulfill the Japanese criteria due to the lack of atopic airway disease, but the pathological evidence of tissue eosinophilia and clinical symptoms suggestive of systemic vasculitis, i.e., lung and neurological involvement, confirmed that the patient had CSS. No patient fulfilled CHCC criteria.

Distribution of peripheral blood eosinophil count and other important laboratory data

The distribution of peripheral blood eosinophilia at diagnosis is shown in Figure 1, with the mean (range) level being 18,108 (3,820-36,760)/μL. That of immunoglobulin E (IgE), C-reactive protein (CRP), and rheumatoid factor (RF) was 2,673 (124-10,695) IU/mL, 51 (0-126) mg/L, and 623.8 (less than 20-3,100) IU/mL, respectively. The normal ranges were <170 IU/mL for IgE, <5 mg/L for CRP, and <20 IU/mL for RF. No relationship was observed between any combination of the four parameters.

Details of the damaged organs

The mean (range) number of damaged organs was 2.7 (1-6). The peripheral nervous system was damaged in all but one patient (n =17, 94%), followed by skin (n =9, 50%), gastrointestinal (GI) tract (n =6, 33%), lung (n =5, 27%), muscles (n =4, 22%), kidney (n =4, 22%), heart (n =3, 17%), and central nervous system (CNS) (n =2, 11%). Table 3 precisely shows which organs were involved in each patient.

PNS involvement almost exclusively consisted of mononeuritis multiplex, mostly diagnosed by physical examination and nerve conduction tests. No patient had the history of diabetes or other collagen/vascular diseases, which could cause the same kind of neuritis. Skin involvement was mostly characterized by palpable purpura and livedo; similarly, CNS involvement was accounted for by diplopia or oculomotor nerve palsy and heart involvement was explained by congestive heart failure or arrhythmia. Angiography was performed in one patient and revealed normal coronary arteries. Cardiac disease was attributed to CSS by autopsy, as described in the later section. GI involvement consisted

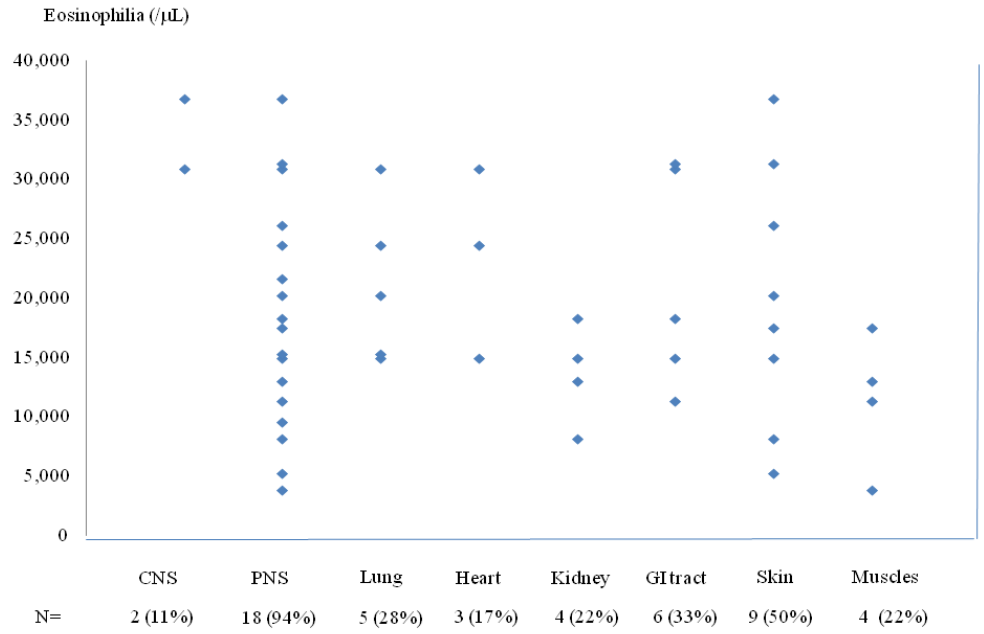

Figure 2. Distribution of the eosinophil count and frequency of each organ involvement. No organ involvement was significantly associated with the level of eosinophilia.

of abdominal pain, vomiting, and diarrhea. Regarding lung involvement, four patients had abnormal lung shadows and one (case 9) had eosinophilic pleuritis. Bronchoalveolar lavage (BAL) was performed in two of the former four patients and the specimens contained markedly increased eosinophils. Culture from sputum, BAL, or pleural effusion was negative.

The distribution of damaged organs and levels of eosinophilia are shown in Figure 2. No significant correlation with eosinophil levels was observed for any of the organs, but CNS involvement tended to be seen among those with a higher count. Likewise, IgE, RF, and CRP levels were not significantly associated with specific organ involvement or the total count of damaged organs.

The patients with heart involvement had a significantly higher number of damaged organs than those without it (4.7(3-6) versus 2.4 (1-3), respectively, mean (range)) (p =0.0018). Significance was maintained even after subtracting the heart from the total number of damaged organs. Involvement of an organ other than the heart was not significantly associated with the number of damaged organs.

MPO-ANCA-positivity and the clinical characteristics

The results of MPO-ANCA did not include five patients, because they were hospitalized before the test had become easily available. Four of the other 13 patients (31%) were positive for MPO-ANCA (Table 2). No difference was observed between those with and without MPO-ANCA, except in the frequency of renal involvement (75% with MPO-ANCA versus 11% without it (p =0.05)).

The significance of LTRA in the occurrence and characteristics of CSS

First, we retrospectively surveyed whether LTRA use elevated the risk of CSS among patients with asthma and found that it did not (3 out of 378 with LTRA versus 7 out of 2,862 without it (p =0.10)).

Next, we surveyed whether LTRA use brings about different clinical features in CSS patients compared with those without LTRA and no characteristic difference was observed.

The details of treatment for CSS

Treatment with glucocorticoids was given to all patients. Ten patients were administered pulsed methylprednisolone (MPSL) (intravenous infusion of MPSL 1 g/day for three days). Daily glucocorticoid treatment was given to all but one patient, who was treated solely with pulsed MPSL. The initial dosage of glucocorticoid was equivalent to 0.8-1.2 mg/kg prednisolone (PSL) for 16 patients and 0.4 mg/kg PSL for one patient. Cyclophosphamide

Table 4. The details of biopsy findings

	PNS	Skin	BM*	Kidney	Lung	Muscles	Testis	GI
A	2	6			1	2	1	
B		1				1	1	
C	4	7	2	1	2	2	1	1
D	8			1		1		
E	1		1			2		
Total	10	7	2	1	2	5	1	1

A: vasculits, B: granuloma, C: eosinophilia, D: findings not inconsistent with CSS other than A, B, or C, E: nonspecific findings

* bone marrow

Table 5. The major autopsy findings in three cases

Case No.	Major autopsy findings
4	1. granulomatous vasculitis with fibrinoid necrosis, glomerular crescent formation, glomerular collapse with necrosis in kidney 2. Vasculitis with fibrinoid necrosis in pancreas, spleen, stomach, liver, PNS, muscle, heart, lung 3. bacterial pneumonia and lung abscess 4. patchy necrosis and sites of fibrosis in cardiac muscles 5. cytomegalovirus infection in GI tract
7.	1. Granulomatous vasculitis with fibrinoid necrosis and tissue eosinophilia in liver, kidney, bronchi, adrenal gland, urinary tract, testis, muscle, PNS, and small intestines. Small-sized arteries, no medium-sized ones, were involved. 2. Eosinophil-rich extravascular granuloma formation in the heart 3.Widespread necrosis of cardiac muscle accompanied by eosinophilia
11.	1. Stones in the gall bladder and common bile duct, accompanied by an abscess formation in the wall of gall bladder 2. hepatocellular carcinoma 3. scar-stage vasculitis in bronchi, lung, GI tract, urinary bladder, pancreas and muscles.

(CYC) was given to two patients, Cases 4 and 13, because both showed resistance to glucocorticoid treatment alone.

Survival outcomes

Four patients had died and 11 were alive on the last date of the research period, while data on 3 patients were not available (Table 3). The direct causes of death were heart failure (n =2), multiple organ failure (n =1), and sepsis due to purulent cholangitis (n =1). All deaths except the case with sepsis were related to CSS and all had cardiac involvement, meaning that all of the patients with heart involvement died (100%), while only one without it showed a fatal outcome (9%). Heart involvement was significantly associated with mortality (p =0.0088), while no other organ damage was associated with it.

Among the patients who had CSS-related deaths, one died of multiple organ failure including progressive dilated cardiomyopathy and one suddenly developed a fatal arrhythmia. Whereas these two died within several months of the disease onset, the other survived for five years despite having impaired cardiac output and a conduction block that required a pacemaker.

Pathological findings derived from biopsies and autopsies

A total of 29 biopsy specimens from 15 patients were available, which included the skin (n =7), sural nerve (n =10), muscle (n =5), lung (n =2), kidney (n =1) GI tract (n =1), and bone marrow aspiration (n =2) (Table 4).

Vasculitis was confirmed in 6 out of 7 skin biopsies (86%), whereas it was confirmed in only 2 of 10 sural nerve biopsied specimens (20%). As for other organs, 2 of 5 muscle (40%) and 1 of 2 lung biopsies (50%), and one testis specimen (100%) included vasculitis, while it was not detected in the GI tract or kidney. Extravascular eosinophilia was observed in 4 of 10 PNS (40%) and 2 of 5 muscle samples (40%), and all of the samples from the skin, bone marrow, kidney, lung, testis, and GI (100%). Eosinophil-rich granulomatous inflammation, regarded as a characteristic pathological finding for CSS, was observed only in 3 samples (skin, testis, and muscle). Other findings to note included crescent formation glomerulonephritis in a renal sample and a high frequency (80%) of asymmetrical and patchy axonal degeneration in sural nerve biopsies, which suggested the preceding presence of vasculitic ischemia.

Three autopsies were performed, and the results are shown in Table 5. It was revealed that all cases showed evidence of vasculitis (including the last- stage ones characterized by the formation of fibtoric scar tissue accompanied by intima proliferation, narrowing or occlusion of the lumen) in many organs. In addition to this, extravascular granuloma was found in the heart of Case 7 together with massive cardiac muscle necrosis and granulomatous vasculitis with fibrinoid necrosis was found in the kidney of Case 4

and many organs including the respiratory tract in Case 7.

Discussion

This is the first case series of Japanese CSS patients including consideration of pathological features. Concerning the basic clinical features, asthma did not precede CSS in two patients. One case did not even have nasal symptoms. CSS without evidence of asthma or upper airway allergic disease has been very occasionally reported[24, 25] and this atypical type should be well-recognized. LTRA use was regarded as being associated with the occurrence of CSS in several studies,[26] but no association was observed in our study.

As noted above, several diagnostic criteria are present and this is occasionally confusing. Almost all of our patients fulfilled ACR and MHLW criteria, but no patient fulfilled CHCC criteria during life because the pathological findings required for CHCC were not derived from the patients, except for an autopsy specimen from Case 7. Our conclusion is that CHCC criteria are too strict to be applied to the actual diagnosis of CSS, as noted by Reid et al.[21]

In general, the clinical features of CSS in our study were mostly similar to those in previous case series,[5-9,20,21,24] but some differences were also observed. Recent findings have proved that at least a part of CSS is associated with ANCA, especially MPO-ANCA[6]. The MPO-ANCA-positive rate was 31% in our series, which was almost comparable to but slightly lower than that of the previous reports (35-78%).[5-9,20-22] We reconfirmed the hypothesis that renal disease is significantly associated with ANCA-positivity.[6,7] However, the presence or absence of ANCA was not associated with heart or peripheral nerve involvement, contrary to previous articles.[20]

CSS has been known to be fatal in severe cases. As with previous reports,[4,5] cardiac involvement was the primary cause of mortality in CSS. The other causes of mortality were multiple organ failure and sepsis in our study, but the patient who died of multiple organ failure had progressive hypokinesis and dilatation of the heart due to CSS cardiomyopathy. CNS involvement, although rare, has been recognized as an important cause of mortality.[3,4,27] Two of our patients suffered from CNS symptoms and both had cranial nerve palsy, which was thought to be related to ischemia due to vasculitis. Both patients recovered following glucocorticoid treatment and none had a poor outcome due to CNS disease. Parenchymal damage such as cerebral hemorrhage or infarction was not observed in our study, and this may have led to the comparably favorable outcome.

It is desirable for pathological investigation to be performed to the greatest extent possible in order to differentiate other eosinophilic diseases from CSS and clarify the its pathogenesis. Vasculitis was observed freqently (86%) in skin tissue and in addition tissue eosinophilia, a relevant finding for the diagnosis, was also observed frequently (100%). Moreover, granuloma was noted in one patient (14%). As skin biopsy is a minimally invasive procedure, it should be positively considered when a patient has dermatological manifestations.

In contrast, neither vasculitis nor extravascular eosinophilia was found in PNS specimens, although findings suggestive of vasculitic damage such as asymmetrical, patchy axonal degeneration were commonly observed. This may be because vessels are affected in a skipped and segmental pattern in CSS and biopsied specimens do not always include positive findings.[2] In addition to this, we have two hypotheses: 1) sural nerve biopsied specimens did not contain sufficient number of small-sized vessels, which are preferentially involved in CSS[2]; 2) extravascular eosinophilia was not easily detectable in nerve tissues compared with other tissues such as the skin. The supporting evidence for 1) might be that the two cases of vasculitis found in PNS consisted of one small-sized and one medium-sized artery, but none of small-sized vessels.

Organ damage related to CSS is thought to result not only from ischemia related to vasculitis but also from the local release of toxic molecules by the infiltrating *eosinophils*, such as cationic proteins, reactive oxygen species, enzymes, proinflammatory *cytokines*, and lipid mediators, which is the mechanism of hypereosinophilic syndrome (HES)-related tissue damage.[23,28] Indeed, CSS has so many overlapping clinical features with HES that it is often difficult to differentiate the two. Recently Horai et al.[29] detected T-cell clones with T-cell receptor rearrangement that are capable of producing a large amount of IL-5, as seen in lymphocytic HES,[30] in a refractory CSS patient, and demonstrated that difficult-to-treat variants of HES could overlap CSS at the molecular level. Unfortunately we could not perform the test in our cases; however, such molecular investigation will surely help us to understand this rare disease with

highly variable clinical courses, especially in terms of treatment for refractory cases.

The initial management of CSS includes high doses of corticosteroids.[3-5,31] CYC is indicated in combination with corticosteroids as part of the first-line treatment when a poor prognosis is expected or as part of second-line treatment should corticosteroids fail or CSS relapse.[3-5,32,33] The five-factors score (FFS) is commonly used as a prognostic index based on the disease severity at onset.[11]

All but two patients (89%) achieved clinical remission with glucocorticoids alone. Remarkably, this included most of the patients with GI involvement (83%) in our study, which was generally regarded as a component of FFS; however, the point to notice is that the original FFS only included severe manifestations, that is, bleeding, perforation, infarction and pancreatitis.[11] Our patients treated by glucocorticoids alone did not meet the GI factor of FFS in the strict sense; on the other hand, one with intractable GI bleeding, a component of FFS, had a fatal outcome despite of CYC use. Serious and refractory GI involvement in CSS patients has been previously reported as well,[34,35] therefore the treatment intensity required for GI symptoms is very variable and is dependent on their severity in each case.

Renal involvement is also regarded as a poor prognostic factor, but this was not confirmed in our study. Two of four patients with renal involvement had proteinuria of 0.5-1 g/day and the other two had proteinuria over 1 g/day. Serum creatinine just before the treatment introduction was increased in two patients but it did not exceed 140 μmol/L, the cutoff for the prediction of a poor prognosis in FFS. The relatively mild symptoms could explain the more favorable outcome in our study, although the two patients with proteinuria in the FFS range were not significantly associated with a poor life prognosis, either. On the contrary, patients with cardiac involvement showed poor prognoses. Unfortunately, most of them were hospitalized in the 1980s and before, when the treatment protocol including CYC was not generally accepted for CSS. The efficacy of CYC was not verified in our study but, considering the severely poor outcome, its use is justified.

We think that the problem with the FFS system lies in the fact that treatment outcomes of primary vasculitides have included all of ANCA-associated vasculitides and polyarteritis nodosa without separating CSS as a distinct entity.[33] As there are important differences in their natural history and prognosis, it is desirable for CSS to be analyzed independently, but very few studies have been reported regarding the appropriate treatment method for CSS alone; in addition, those studies were done among limited patient subsets and they did not reflect the overall characteristics of the patients.[33] Our data implied that most of CSS patients, at least among the Japanese, can be initially treated by glucocorticoids alone, unless they are affected by cardiac involvement.

In conclusion, we reported 18 patients with CSS with pathological considerations. This is the first case series report from Japan in the English literature. We hope to advance knowledge of this rare syndrome through this report.

Acknowledgement

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