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CLINICAL INVESTIGATION

Clinical characteristics of scleritis patients with emphasized comparison of associated systemic diseases (anti-neutrophil cytoplasmic antibody-associated vasculitis and rheumatoid arthritis)

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Abstract

Purpose We evaluated patient profiles, clinical features, associated systemic diseases, treatment modalities, and ocular complications in cases of scleritis and episcleritis.

Study design Retrospective.

Methods Clinical data of 128 patients referred to the ophthalmology clinic at Jichi Medical University Hospital during the 4-year period from April 2011 to March 2015, and diagnosed with scleritis or episcleritis were examined. Gender, average onset age, unilateral or bilateral manifestation, classification type, associated systemic diseases, and treatments were retrospectively investigated.

Results The cohort consisted of 57 men and 71 women. Average onset age was 54.3 ± 17.4 years. Diffuse anterior scleritis was the most common type. It was noted in 43 (32.8%) patients, followed by episcleritis in 35 (27.3%), nodular anterior scleritis in 23 (18.0%), necrotizing anterior scleritis in 22 (17.2%), and posterior scleritis in 6 (4.7%). Eighteen (81.8%) of 22 patients with necrotizing anterior scleritis required some type of systemic medication, including corticosteroid, cyclophosphamide, cyclosporine, azathioprine, methotrexate, or rituximab administration. Forty (31.3%) had associated systemic diseases, which included 10 with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis and 8 with rheumatoid arthritis (RA). Patients with ANCA-associated vasculitis had a tendency to develop scleritis first and had significantly worse visual prognoses compared to those with RA.

Conclusions Approximately 30% of the patients with scleritis and episcleritis had complications involving systemic diseases, including ten patients with ANCA-associated vasculitis and 8 with RA. ANCA-associated vasculitis was more often diagnosed after scleritis and patients suffered poorer visual prognoses than those with RA.

Keywords Scleritis · Episcleritis · Rheumatoid arthritis · Anti-neutrophil cytoplasmic antibody (ANCA) · ANCA-associated vasculitis

Introduction

Scleritis, inflammation of the sclera, often poses a significant threat to vision. The disease is typically characterized by severe painful lesions located in the sclera, which may also involve the cornea and even the underlying uvea. Episcleritis, on the other hand, is inflammation confined to the superficial episcleral tissue. It does not involve the deep episcleral tissue that overlies the sclera and is a milder form of ocular inflammation that is not sight-threatening [1].

The Watson classification system [1, 2] classifies scleritis into three types: episcleritis, anterior scleritis and posterior scleritis. Episcleritis is caused by inflammation of the superficial layer of the sclera, while anterior scleritis

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is caused by inflammation in deeper layers of the anterior portion of the sclera. Furthermore, anterior scleritis is sub-classified into nodular anterior, diffuse anterior, and necrotizing anterior scleritis, with the latter associated with scleromalacia perforans. Posterior scleritis is inflammation of the sclera in the area posterior to insertion of the rectus muscles. Since posterior scleritis and Vogt-Koyanagi-Harada disease (VKH) exhibit similar fundal characteristics, it is often difficult to differentiate the two. Patients with posterior scleritis rarely show systemic disease, while those with VKH usually develop aseptic meningitis, labyrinthitis, vitiligo, or poliosis. Anterior scleritis and episcleritis are types of refractory autoimmune or infectious inflammation; both are accompanied by conjunctival and surface or deeper scleral vascular congestion.

Rheumatoid arthritis (RA), relapsing polychondritis, anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis, and polychondritis are known as systemic autoimmune diseases that induce scleritis or episcleritis. Tuberculosis, syphilis, and herpes virus infection are also known as infectious origins [3, 4]. Systemic vasculitic diseases associated with the presence of marker antibodies (ie, c- and p-ANCA) are collectively referred to as ANCA-associated vasculitis, including granulomatosis with polyangiitis (GPA, formerly called Wegener's granulomatosis), microscopic polyangiitis (MPA), and allergic granulomatous angiitis (AGA) [5]. Refractory ANCA-positive vasculitis is treated with immunosuppressive agents, such as cyclophosphamide, cyclosporine, azathioprine, or methotrexate in addition to corticosteroids. Moreover, rituximab, chimeric murine/human monoclonal IgG1 kappa antibody directed against the CD20 antigen, has recently been shown effective for maintenance of ANCA-associated vasculitis [6, 7].

Topical medication, together with immunosuppressive agents that are often necessary, is generally administered for scleritis and episcleritis associated with systemic autoimmune diseases. Antibiotic or antivirus agents along with topical and/or immunosuppressive agents are also given for those associated with infectious diseases. Recently, Cyclosporine has been approved as an agent for non-infectious uveitis and scleritis in Japan. Some cases of scleritis associated with systemic autoimmune diseases may become refractory to high-dose corticosteroids or immunosuppressive agents. Patients with refractory or recurrent scleritis often suffer from secondary cataracts or glaucoma.

We examined clinical data of outpatients with scleritis who were referred to the ophthalmology clinic of Jichi Medical University Hospital. From our findings, we investigated the tendency of each classification type in relation to patient characteristics, clinical features, associated systemic diseases, ocular complications, and treatment modalities.

Materials and methods

This retrospective study was approved by the ethics committee of Jichi Medical University Hospital. Clinical data of 128 outpatients referred to the ophthalmology clinic of Jichi Medical University Hospital during the 4-year period from April 2011 to March 2015, and diagnosed with episcleritis or scleritis were retrospectively examined. Factors noted included gender, age of onset, unilateral or bilateral manifestation, classification type, treatments during observation period, ocular history of cataract surgery and extended ocular hypertension (EOH), and associated systemic diseases.

Classification type was determined according to the Watson classification system [1, 2]. Magnetic resonance imaging (MRI) and/or ultrasonography were performed to confirm the thickness of posterior sclera to facilitate the diagnosis of posterior scleritis. To rule out VKH, fluorescein angiography was conducted when necessary. Patients with only uniocular involvement before and during the observation period were defined as uniocular. For classification of anterior scleritis, patients who showed more than 1 type during the observation period or different classification types of bilateral anterior scleritis, were classified according to the following priority: necrotizing anterior scleritis, diffuse anterior scleritis, nodular anterior scleritis, or episcleritis.

In cases without systemic autoimmune diseases, who may or may not develop systemic diseases later on, patients with non-infectious scleritis or episcleritis received full investigation for underlying systemic diseases, including blood testing (c-ANCA and p-ANCA), repeated as necessary. To diagnose infectious diseases that may cause scleritis, Tuberculin skin testing and/or interferon gamma release assay, chest x-ray, serologic tests for syphilis and herpes viral antibody tests were conducted. Except for a few patients, all were treated following the ladder-step approach reported by Tanaka R et al. [8]. Furthermore, each patient was referred to an internal physician and examined for the presence of systemic diseases associated with episcleritis or scleritis. Scleritis and episcleritis as one symptom of uveitis (sarcoidosis, VKH, Behcet disease etc.) were excluded from this study. As for ocular complications during the observation period, those who underwent cataract surgery were classified in the cataract surgery group. Those treated with eye drops or systemic medication for ocular hypertension longer than 1 month during the observation period were considered to suffer EOH. Those who were already diagnosed with certain systemic diseases and developed scleritis were referred to us and treated for ocular conditions accordingly.

Statistical analysis

Statistical analysis was performed using Student's unpaired t-test or the chi-square test. Values of $p < 0.05$ were

considered to be statistically significant. All statistical analyses were performed with SPSS for Windows, version 12.0 (SPSS Inc.). Values are shown as the mean ± standard deviation (S.D.). Best-corrected visual acuity (BCVA) less than 20/200 was defined as poor.

Results

There were 85 patients with uniocular and 43 with binocular involvement. Men numbered 57 (uniocular 41, binocular 16) and women 71 (uniocular 44, binocular 27). The average age of ocular onset for all patients was 54.3 ± 17.4 years old (53.7 ± 17.4 for men and 54.8 ± 17.5 years for women; $p = 0.36$, Student's t-test).

Scleritis classification

Diffuse anterior scleritis was classified in 32.8% of all patients (42/128), followed by episcleritis in 27.3% (35/102), nodular anterior scleritis in 18.0% (23/128), necrotizing anterior scleritis in 17.2% (22/128), and posterior scleritis in 4.7% (6/128) (Table 1). Ratios for gender and uniocular or binocular involvement for each type are also shown in Table 1. The average age of ocular onset of necrotizing anterior scleritis (67.7 ± 14.2 years) was significantly older than that of diffuse anterior scleritis (52.2 ± 16.3 years) and nodular anterior scleritis (53.6 ± 16.1 years) ($p = 0.00013 < 0.025$ and $p = 0.0016 < 0.025$, respectively, Student's t-test by Bonferroni correction).

Treatments for each classification type

Systemic combination treatment with immunosuppressive agents were considered, decided, and administered by internists. There was a tendency to use more immunosuppressive agents for severer scleritis cases, such as necrotizing anterior scleritis, as compared to milder scleritis, such as episcleritis and nodular anterior scleritis (Table 2). Three patients with posterior scleritis were treated with topical and/or systemic corticosteroid administrations, 2 of whom received only systemic corticosteroid therapy and 1 was treated with triamicinolone acetonide injections into the sub-tenon space. Six patients received Rituximab treatment and 2 patients received adalimumab.

Ocular complications

Six patients underwent cataract surgery (Table 3). Twenty patients were treated for EOH longer that 1 month during the observation period. Patients with diffuse anterior scleritis who suffered from EOH showed the highest frequency (31.0%, 13/42). None underwent glaucoma surgery during the observation period and only 1 received cataract surgery, including vitrectomy for an epiretinal membrane, prior to the onset of scleritis. Following the onset of scleritis, 3 patients with diffuse anterior scleritis, 2 with necrotizing anterior scleritis, and 1 with nodular anterior scleritis underwent cataract surgery.

Associated systemic diseases

Ten patients with ANCA-associated vasculitis and 8 with rheumatoid arthritis (RA) were identified (Tables 4, 5). As for systemic diseases associated with each type, there was a tendency for ANCA-associated vasculitis to be more frequently detected in patients with diffuse or necrotizing anterior scleritis as compared to the other types (Tables 4, 5). All patients with posterior scleritis were idiopathic, i.e., no relationship could be detected with any systemic diseases.

Additionally, we compared the profiles of 10 ANCA-associated vasculitis patients with 8 patients with RA (Table 5). There were no significant differences regarding age of ocular onset ($p = 0.5$, Student's unpaired t-test), observation period concerning ocular inflammation ($p = 0.40$, Student's unpaired t-test), male to female ratio (4:6, 3:5, $p = 0.91$, chi-square test), or ratio of monocular and binocular involvement (5:5, 4:4, $p = 1$, chi-square test) between the two groups. In addition, there was no significant difference ($p = 0.28$, chi-square test) in the

Table 1 Profiles of patients with different scleritis types

Type	No. (%)	Male:female	Uniocular:binocular	Average onset age
Episcleritis	35 (27.3)	12:23	20:15	47.3±17.9
Nodular anterior scleritis	23 (18.0)	12:11	20:3	53.6±16.1*
Diffuse anterior scleritis	42 (32.8)	22:20	26:16	52.2±16.4^{++}
Necrotizing anterior scleritis	22 (17.2)	8:14	13:9	67.7±14.2 *$^{++}$
Posterior scleritis	6 (4.7)	3:3	5:1	64.5± 8.5
Total	128 (100)	57:71	84:44	54.3±17.4

The average onset age of patients with necrotizing anterior scleritis was significantly older than that of those with nodular anterior scleritis (*) or diffuse anterior scleritis (++)

*$p = 0.0160 < 0.025$, ++$p = 0.0078 < 0.025$, t-test with Bonferroni correction

Table 2 Treatments for scleritis types

Treatment pattern		Episcleritis	Nodular	Diffuse	Necrotizing	Posterior	Total
Topical only (n = 63)	Topical CSO only	26	12	20	4	1	63
Single oral agent (n = 52)	Oral NSAID only	0	0	1	0	0	1
	Topical NSAID + oral CSO	1	0	0	0	0	1
	Oral CSO only	1	1	1	0	2	5
	Topical CSO + oral SASP	1	0	0	0	0	1
	Topical& oral CSO	6	7	14	13	3	43
	Topical CSO + oral CY	0	0	1	0	0	1
Two oral agents (n = 9)	Topical& oral CSO + oral SASP	0	0	0	1	0	1
	Oral CSO + oral CY	0	0	1	0	0	1
	Topical& oral CSO + oral CY	0	0	0	1	0	1
	Topical& oral CSO + oral EX	0	0	1	0	0	1
	Topical& oral CSO + oral AZ	0	2	0	1	0	3
	Topical & oral CSO + oral MTX	0	1	1	0	0	2
Oral agent(s) and monoclonal antibody (n = 4)	Topical& oral CSO + Rit	0	0	0	1	0	1
	Topica l& oral CSO + oral EX + Rit	0	0	1	0	0	1
	Topical & oral CSO +systemic MTX + Rit	0	0	0	1	0	1
	Topical& oral CSO + oral MTX + ADA	0	0	1	0	0	1
Total		35	23	42	22	6	128

CSO: corticosteroid (topical or oral), EX: cyclophosphamide (oral), CY: cyclosporine (oral), MTX: methotrexate (oral), AZT: azathioprine (oral), SASP: salazosulfapyridine (oral), ADA: adalimumab (intravenous injection), Rit: rituximab (intravenous injection)

Table 3 Ocular complications among scleritis types

Ocular complication	Total (n = 128)	Episcleritis (n = 35)	Nodular (n = 23)	Diffuse (n = 42)	Necrotizing (n = 22)	Posterior (n = 6)
Cataract surgery	6 (4.7)	0 (0)	1 (4.3)	3 (7.1)	2 (9.1)	0 (0)
EOH	22 (17.2)	2 (5.7)	2 (8.7)	13 (31.0)	4 (18.2)	1 (16.7)
	Number (%)					

Cataract surgery: number of patients who underwent cataract surgery during observation period

Each cataract surgery was performed after 3 or longer months of quiescent period

EOH (extended ocular hypertension): number of patients treated with eye drops or systemic medication for ocular hypertension for longer than 1 month during observation period. No patient received glaucoma surgery during this period

**Percentage of patients with each ocular complication among patients with each scleritis type; number/N × 100%

frequency of necrotizing anterior scleritis (5/10, 50.0% vs. 2/8, 25.0%). Moreover, 2 patients (20%) with ANCA-associated and 4 (50%) with RA suffered EOH. One patient (10%) with ANCA-associated vasculitis underwent cataract surgery during the observation period after the onset of scleritis, while no one (0%) with RA required cataract surgery. There was no difference in ocular complications between patients with ANCA-associated vasculitis (p = 0.18) and those with RA (p=0.36, chi-square test). In contrast, when visual acuity at the end of the ocular observation period was analyzed, the percentage of eyes with poor visual acuity (BCVA<20/200) in patients with ANCA-associated vasculitis (8/16 eyes, 50.0%) was significantly (p = 0.0042, chi-square test) higher than that in patients with RA (0 eyes/12 eyes, 0.0%). Moreover, there was also a significant difference between the two groups in the ratio of patients diagnosed before ocular onset as compared to after ocular onset (5:5 vs. 8:0, p = 0.019, chi-square test) (Table 5). All patients with RA were diagnosed before ocular onset of scleritis, and preserved good vision during the observation period. Half of patients with ANCA-associated vasculitis were diagnosed after scleritis and their visual prognoses were poor, often resulting in blindness, while those who were diagnosed before scleritis preserved fair vision.

Table 4 Relationships among associated systemic diseases and scleritis types

Associated systemic disease	Total	Episcleritis	Nodular	Diffuse	Necrotizing	Posterior
ANCA associated vasculitis	10	2	2	1	5	0
Rheumatoid arthritis	8	2	0	4	2	0
Hematological malignant diseases	4	1	0	3	0	0
Herpesvirus infection	3	2	0	1	0	0
Ulcerative colitis	3	1	2	0	0	0
Systemic lupus erythematosus	2	1	0	1	0	0
Hepatitis C virus infection	2	1	1	0	0	0
Relapsing polychondritis	1	0	0	1	0	0
Pemphigus	1	0	0	1	0	0
Interstitial pneumonitis	1	1	0	0	0	0
Interstitial nephritis	1	1	0	0	0	0
Gout	1	1	0	0	0	0
Still's disease	1	1	0	0	0	0
Psoriasis	1	0	0	1	0	0
Malignant tumor	1	0	0	0	1	0
Total	40	14	5	13	8	0

The 4 patients with hematological malignant diseases were comprised of 3 with leukemia and 1 with a lymphoma

Malignant tumor: pancreatic cancer

Discussion

On certain occasions both scleritis and episcleritis are classified as types of uveitis. A recent prospective epidemiologic survey of uveitis conducted in Japan [9] found that the frequency of patients with scleritis among all patients with uveitis was 6.1%, following sarcoidosis (10.6%), Vogt-Koyanagi-Harada disease (7.0%), and acute anterior uveitis (6.5%). Scleritis and episcleritis are frequently observed and treated as ocular inflammatory diseases in Japan.

As with previous reports [8, 10–12], the present findings (Table 1) revealed that diffuse anterior scleritis was the most frequent and posterior scleritis the most infrequent among the examined cases. Among the ocular complications (Table 3), 13 (31.0%) of 42 patients with diffuse anterior scleritis experienced EOH and 4 (18.2%) of 22 with necrotizing anterior scleritis had EOH. None received filtering operation. This might reflect some difficulties in this procedure being applied to a diseased sclera. Moreover, 3 (7.1%) of those 42 patients with diffuse anterior scleritis and 2 (9.1%) of the 22 with necrotizing anterior scleritis underwent cataract surgery during the observation period. These results seem to reflect how topical and/or systemic corticosteroid therapy were administered in patients with diffuse or necrotizing anterior scleritis, as compared to other types of scleritis. In fact, 9 (25.7%) of 35 patients with episcleritis were treated not only with topical corticosteroid but also systemic medications, while 22 (52.4%) of 42 with diffuse anterior scleritis and 18 (81.8%) of 22 with necrotizing anterior scleritis were treated with both modalities (Table 2).

Previous investigations of associated systemic diseases report identification of certain systemic diseases in 20-50% of Japanese patients with scleritis (excluding episcleritis), with the most common being RA (21.7%), followed in order by relapsing polychondritis (3.6%), autoimmune thyroiditis (3.6%), ankylosing spondylitis (1.2%), systemic lupus erythematosus (1.2%), and ANCA -associated vasculitis (1.2%). In the presence cohort, associated systemic diseases were identified in 31.3% of our patients, similar to previous reports [1, 3, 9], among which the most common was ANCA-associated vasculitis (10/128, 7.8%), followed by RA (8/128, 6.3%), and hematological malignant diseases (4/128, 3.1%) (Table 4). Of those 4 patients with hematological malignant diseases, 3 were shown to have leukemia and 1 lymphoma. It is known that patients with leukemia or lymphoma can develop scleritis or episcleritis, though such occurrences are infrequent [13, 14].

Compared with prior investigations, the present results indicate that ANCA-associated vasculitis is being diagnosed more frequently. Previous studies conducted in Japan report that the number of GPA cases increased by 1.5 times from 1994 to 2006, and those with MPA or polyarteritis nodosa (PAN) by 2.5 [5]. Therefore, it can be speculated that the number of patients with ANCA-associated vasculitis including MPA and GPA is increasing in Japan. Moreover, it is reported that nearly 20 % of patients with scleritis were ANCA-positive [15, 16]. Systemic vasculitis diseases, such as GPA and PAN, were less likely than other rheumatic diseases to have been previously diagnosed [3]. Among our patients, 3 were ANCA-positive in blood findings obtained at the first

Table 5 Profiles of 10 patients with ANCA-associated vasculitis and 8 with rheumatoid arthritis

Pt. no.	Gender	Age (years)	Type of scleritis	Uniocular or Binocular	Period (months)	Before or After	VA	Treatment	Systemic disease, complications
(a) ANCA-associated vasculitis (10 patients, 16 eyes)									
1.	f	46	necrotizing	Binocular	48	Before	20/20 null	topical& oral CSO + oral MTX + Rit	GPA
2.	f	76	necrotizing	Binocular	48	After	null 20/25	topical & oral CSO	MPA cat ope, EOH
3.	m	66	nodular	Uniocular	3	Before	20/20	topical & oral CSO + oral AZT	GPA
4.	f	68	necrotizing	Uniocular	26	After	null	topical & oral CSO + Rit	GPA EOH
5.	f	57	episcleritis	Binocular	1	Before	20/20 20/20	topical & oral CSO	RPGN
6.	f	74	necrotizing	Binocular	42	After	20/200 null	topical & oral CSO	MPA
7.	f	72	episcleritis	Binocular	16	After	20/500 null	topical & oral CSO	GPA
8.	m	71	nodular	Uniocular	10	Before	20/20	topical & oral CSO + oral AZT	MPA
9.	m	40	diffuse	Binocular	4	Before	20/20 20/20	topical& oral CSO + oral EX + Rit	GPA
10.	m	70	necrotizing	Uniocular	12	After	20/400	topical & oral CSO + oral AZT	GPA
average ± S.D.		64.0 ± 12.3			21.0 ± 17.8				
								topical only: 0	
		ratio of Uniocular to Binocular = 4:6						single oral agent: 4	
		ratio of <Before> to <After> = 5:5						ratio of good to poor visual acuity = 8:8	
		ratio of good to poor visual acuity = 8:8						oral agents and Rit: 3	
(b) Rheumatoid arthritis (8 patients, 12 eyes)									
1.	f	60	diffuse	Uniocular	37	Before	20/20	topical & oral CSO	RA
2.	f	64	necrotizing	Uniocular	48	Before	20/25	topical & oral CSO + oral SASP	RA, cat ope, EOH
3.	m	61	diffuse	Uniocular	29	Before	20/20	topical & oral CSO + oral SASP	RA EOH
4.	f	77	diffuse	Binocular	1	Before	20/20 20/20	topical & oral CSO	RA EOH
5.	f	43	episcleritis	Binocular	9	Before	20/20 20/20	topical NSAID + oral CSO	RA
6.	m	51	episcleritis	Uniocular	9	Before	20/20	topical CSO + oral SASP	RA

Table 5 (continued)

Pt. no.	Gender	Age (years)	Type of scleritis	Uniocular or Binocular	Period (months)	Before or After	VA	Treatment	Systemic disease, complications
7.	f	68	diffuse	Binocular	11	Before	20/20 20/20	topical & oral CSO + oral MTX	RA EOH
8.	m	88	necrotizing	Binocular	8	Before	20/50 20/60	topical &oral CSO	RA
average ± S.D.		64.0±14.1			19.0±15.7				
		ratio of Uniocular to Binocular = 4 : 4 ratio of <Before> to< After> = 8 : 0 ratio of good to poor visual acuity = 12 : 0						topical only: 0 single oral agent: 5 two oral agents: 3	

f: female, m: male, age: age of ocular onset (years)

Period: follow-up period concerning ocular inflammation (months)

Before: ANCA or RA was diagnosed previously before ocular onset

After: ANCA or RA was diagnosed during follow-up period after ocular onset

VA: best corrected visual acuity at the end of ocular observation period

Systemic disease: scleritis-associated systemic disease

Complications: ocular complications during observation period

CSO: corticosteroid, MTX: methotrexate, EX: cyclophosphamide, AZT: azathioprine

SASP: salazosulfapyridine

GPA: granulomatosis with polyangiitis, MPA: microscopic polyangiitis

RPGN: rapidly progressive glomerulonephritis

EOH: extended ocular hypertension during ocular observation period

cat ope: cataract surgery performed during ocular observation period

±: average ± standard deviation

Rit: rituximab

There were no significant differences between patients with ANCA-associated vasculitis and those with RA, for age of ocular onset ($p = 0.5$, Student's unpaired t-test), follow-up period regarding ocular inflammation ($p = 0.40$, Student's unpaired t-test), and ratio of uniocular to binocular involvement ($p = 1$, chi-square test). However, as compared to patients with RA, those with ANCA-associated vasculitis showed a significantly greater frequency for diagnosis during the follow-up period after ocular onset ($p = 0.019$, chi-square test) and poor visual acuity ($p = 0.0042$, chi-square test)

visit and yet could not be diagnosed with ANCA-associated vasculitis. They may be diagnosed with ANCA-associated vasculitis in the future, though during the observation period they did not show any systemic signs of ANCA-positive vasculitis. Scleritis due to ANCA-associated vasculitis might be increasing in frequency. In the present study, we found a tendency in patients with scleritis due to ANCA-associated vasculitis to have worse visual prognoses and require more aggressive therapy as compared to patients with scleritis due to RA. However, there was no significant difference between patients with both diseases in regard the ratio of necrotizing anterior scleritis, ratio of uniocular to binocular, and follow-up period (Table 5). These tendencies correspond to previous reports [15, 17–20] showing that patients with scleritis due to ANCA-positive vasculitis tend to have worse visual prognosis and are more refractory to treatment for other systemic diseases such as RA. It is also reported that patients with necrotizing anterior scleritis tend to have worse visual prognosis as compared to those with other types of scleritis [21, 22]. Among the patients with necrotizing anterior scleritis in the present investigation, there was no significant difference ($p = 0.28$, chi-square test) between ANCA-associated vasculitis (5/10, 50%) and RA (2/8, 25%). On the other hand, our findings correspond with those of a previous report by Akpek et al. [3] stating that ANCA-associated vasculitis was less likely to be diagnosed before ocular onset. Worse visual prognosis for patients with scleritis due to ANCA-associated vasculitis might be related to this tendency for ANCA-associated vasculitis not to be diagnosed before ocular onset. Consequently, it is speculated that such a tendency might result in a delay until the patients receive adequate aggressive therapy, resulting in the progression of scleral necrotizing often seen in patients with ANCA-associated vasculitis. Patients no. 4 and 6 were diagnosed with ANCA-associated vasculitis after ocular

onset and became blind due to necrotizing scleritis. Moreover, Patient no. 1 with ANCA-associated vasculitis became blind due to ischemic optic neuropathy.

Rituximab, an anti-CD20 monoclonal antibody, was recently reported to be effective for systemic treatment of ANCA-associated vasculitis [6, 7]. Suhler et al. [23] found that the drug was effective in 9 of 12 patients as treatment for refractory noninfectious scleritis due to systemic diseases, such as GPA, RA, and others. In our investigation, 3 of 10 patients with scleritis due to ANCA-associated vasculitis were treated with rituximab in addition to other agents (Table 5a). Two of 5 eyes in 3 patients treated with rituximab had poor visual acuity.

Limitation of our work: because of the low number of patients treated at a single institution in Japan, clinical outcomes referred to in our work might not apply to other ethnic groups. A large-scale study of patients treated with rituximab is required to elucidate its effectiveness as medication for refractory noninfectious scleritis. We also had no opportunity to obtain data regarding the severity of scleritis, as in Modified McKulskey grading system [24], as well as other detailed ocular complications than investigated in the manuscript.

In summary, approximately 30% of the present patients with scleritis and episcleritis also had systemic diseases, of which ANCA-associated vasculitis was the most frequent and resulted in poor visual prognosis. ANCA-associated vasculitis was often diagnosed after scleritis, and therefore must be kept in mind as a possible associated systemic disease.

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