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ORIGINAL PAPER

Ocular inflammation associated with relapsing polychondritis in Japanese patients: a review of 11 patients

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Abstract
Purpose To investigate the clinical features of patients with ocular inflammation associated with relapsing polychondritis in Japan.
Methods Ocular findings, systemic symptoms, and therapies were analysed retrospectively.
Results Nine of 11 patients had scleritis (diffuse scleritis: six patients, posterior scleritis: two patients, episcleritis: one patient) and two patients had anterior uveitis. All cases were bilateral, and ten patients experienced recurrent episodes. Auricular chondritis was the most common systemic symptom. Ten patients were administered systemic steroids, and five patients were administered other immunosuppressive medications for severe systemic symptoms. At their last visit, none of the patients had decreased visual acuity that resulted from relapsing polychondritis-associated ocular inflammation.
Conclusions Ocular inflammation is often bilateral and recurring. Patients with ocular inflammation must be questioned regarding systemic symptoms so that the signs of relapsing polychondritis are not overlooked. Early diagnosis and prompt, appropriate treatment are important because relapsing polychondritis is a potentially lethal disease.

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Keywords Ocular inflammation · Relapsing polychondritis · Scleritis · Treatment · Uveitis

Introduction

Relapsing polychondritis (RP) is a rare autoimmune disease that is characterized by recurrent episodes of inflammation of the cartilaginous tissues throughout the body, including the external ears, nose joints, and respiratory tract. Other proteoglycan-rich tissues such as the eyes, inner ear, heart, and blood vessels can also be affected [1, 2]. The incidence of RP in Rochester, MN, USA, has been estimated to be 3.5 cases, per million of the population, per year [2], and the prevalence of RP in Japan has been estimated to be the same [3].

According to published reports, 9–32% of RP patients have ocular symptoms at the onset of RP and 46–65% develop ocular symptoms during the course of the disease [3–6]. Episcleritis/scleritis and conjunctivitis are the most common ocular symptoms of RP [4–7]. Although RP is a rare disease, it is one of the major causes of scleritis, and previous studies have reported that 1.9–4.9% of scleritis is caused by RP [8–11].

There have been several large-scale reports from the USA and Europe on the ocular manifestation of RP [4–6, 12]. Although there has been one large-scale

survey of patients with RP from Japan, this report contains only the numbers of patients with ocular inflammation and the types of ocular inflammation found, without the mention of specific details on ocular inflammation-associated RP [3]. Other than this, there are few case reports on this subject in Japan [13–16].

In the present study, we investigated the clinical features, associated systemic diseases, and treatment of Japanese patients with ocular inflammation caused by RP.

Patients and methods

We retrospectively reviewed the clinical course and clinical findings of consecutive patients with RP-associated ocular inflammation who had visited the uveitis clinic of the University of Tokyo Hospital for the first time between January 2000 and December 2017. All cases received a diagnosis of RP based on the Damiani criteria [17]. Other types of ocular inflammation based on ocular and systemic symptoms, as well as laboratory examinations, were excluded. The Damiani criteria are a modified version of McAdam's criteria [4]. McAdam's criteria require the presence of three of the following six clinical features: bilateral auricular chondritis, non-erosive seronegative inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis, or audiovestibular damage. The Damiani criteria include three McAdam's criteria: one McAdam criterion and positive histological confirmation, or two McAdam's criteria and response to corticosteroids or dapsone. Medical records were retrospectively examined to investigate sex, age (at initial visit, RP onset, and ocular inflammation onset), type of ocular inflammation, recurrence episodes, observation period, laterality, corrected visual acuity (at initial visit and last visit), anterior segment findings and funduscopic findings during follow-up, ocular complications related to RP, other complicated systemic immune-mediated diseases (SIMD), systemic symptoms, and topical and systemic treatments. The Watson and Hayreh classification was used for determining the subtype of scleritis [18], and the grading system for scleritis (Grades 0–4) was used for the evaluation of scleral inflammation [19]. Visual acuity was determined using a standard Landolt VA chart.

This retrospective study was approved by the ethics committee of the University of Tokyo Hospital and conforms to the provisions of the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Results

Table 1 displays the demographic characteristics of the 22 eyes of the 11 cases (four males and seven females; 48.5 ± 20.5 years old at initial visit; range 18–75 years old) included in the present study. The observation period was 41.5 ± 46.1 months (range 4–130 months), and all cases were bilateral. The types of ocular inflammation observed included diffuse scleritis (six patients), posterior scleritis (two patients), episcleritis (one patient), and anterior uveitis (two patients). Out of six patients with anterior scleritis, half exhibited Grade 3 scleral inflammation and the rest exhibited Grade 2 scleral inflammation. Of the two patients with anterior uveitis, one patient showed anterior chamber cells, fine keratic precipitates, and ciliary injection (Patient 10) and the other patient showed anterior chamber cells without keratic precipitates (Patient 11). Ten patients (90.9%) experienced recurrent episodes. Ocular complications observed in the patients included cataract in three patients; disc swelling in two patients; steroid-induced ocular hypertension in two patients; macular oedema in one patient (Fig. 1a); scleral thinning in one patient (Fig. 2d); and vitreous opacity in one patient (Fig. 1b). Of the eight patients with scleritis, two patients showed associated anterior chamber inflammation. Further, of the two patients with steroid-induced ocular hypertension, one patient required trabeculotomy on both eyes (Patient 1) and the other patient's ocular hypertension was resolved after reducing the dose of her corticosteroid eye drops (Patient 5). The visual prognosis was good for almost all the patients. Decreased vision was found in Patients 6 and 9 due to causes unrelated to RP-associated ocular inflammation (Patient 6: psychogenic reason; Patient 9: diabetic retinopathy). One of the 11 patients (9.1%) with RP-associated ocular inflammation had systemic lupus erythematosus (SLE) (Patient 10).

Table 2 shows the systemic symptoms. Ocular inflammation was the initial presenting manifestation in six patients. In these six patients, the average

Table 1 Demographics of ocular inflammation associated with RP

No.	Sex	Age at initial visit	Follow-up (month)	Age of RP onset	Age of ocular inflammation onset	Administration of systemic therapy from ocular inflammation onset (month)	Laterality	Type of inflammation	Recurrences of ocular inflammation	VA at initial visit OD, OS	VA at final visit OD, OS	Ocular complication related to RP
1	M	18	99	16	16	23	B	Diffuse scleritis (Grade 3)[a]	+	6/4, 6/4	6/5, 6/5	Steroid-induced OH, scleral thinning
2	F	35	4	29	32	–	B	Diffuse scleritis (Grade 2)[a]	+	ND, ND	6/4, 6/4	Anterior uveitis
3	F	45	99	35	43	28	B	Diffuse scleritis (Grade 2)[a]	+	6/4, 6/4	6/5, 6/5	–
4	F	49	10	49	49	2	B	Diffuse scleritis (Grade 3)[a]	+	6/4, 6/4	6/4, 6/4	–
5	F	19	52	19	19	1	B	Diffuse scleritis (Grade 2)[a]	+	6/4, 6/4	6/5, 6/5	Anterior uveitis, steroid-induced OH
6	F	48	10	48	48	4	B	Diffuse scleritis (Grade 3)[a]	+	6/6, 6/5	6/12, 6/12	–
7	M	68	20	68	68	0	B	Posterior scleritis	–	6/7, 6/15	6/7, 6/10	Cataract
8	F	71	10	71	71	7	B	Posterior scleritis	+	6/6, 6/5	6/5, 6/5	Vitreous opacity, disc swelling, macular oedema
9	M	70	14	70	70	4	B	Episcleritis	+	6/5, 6/67	6/10, 6/7	–
10	M	36	130	35	36	0	B	Anterior uveitis	+	6/6, 6/7	6/7, 6/7	Cataract, disc swelling
11	F	75	8	73	73	28	B	Anterior uveitis	+	6/7, 6/100	6/6, 6/10	Cataract

RP relapsing polychondritis, *OH* ocular hypertension, *VA* visual acuity; *ND* no data

[a]Grade of scleral inflammation

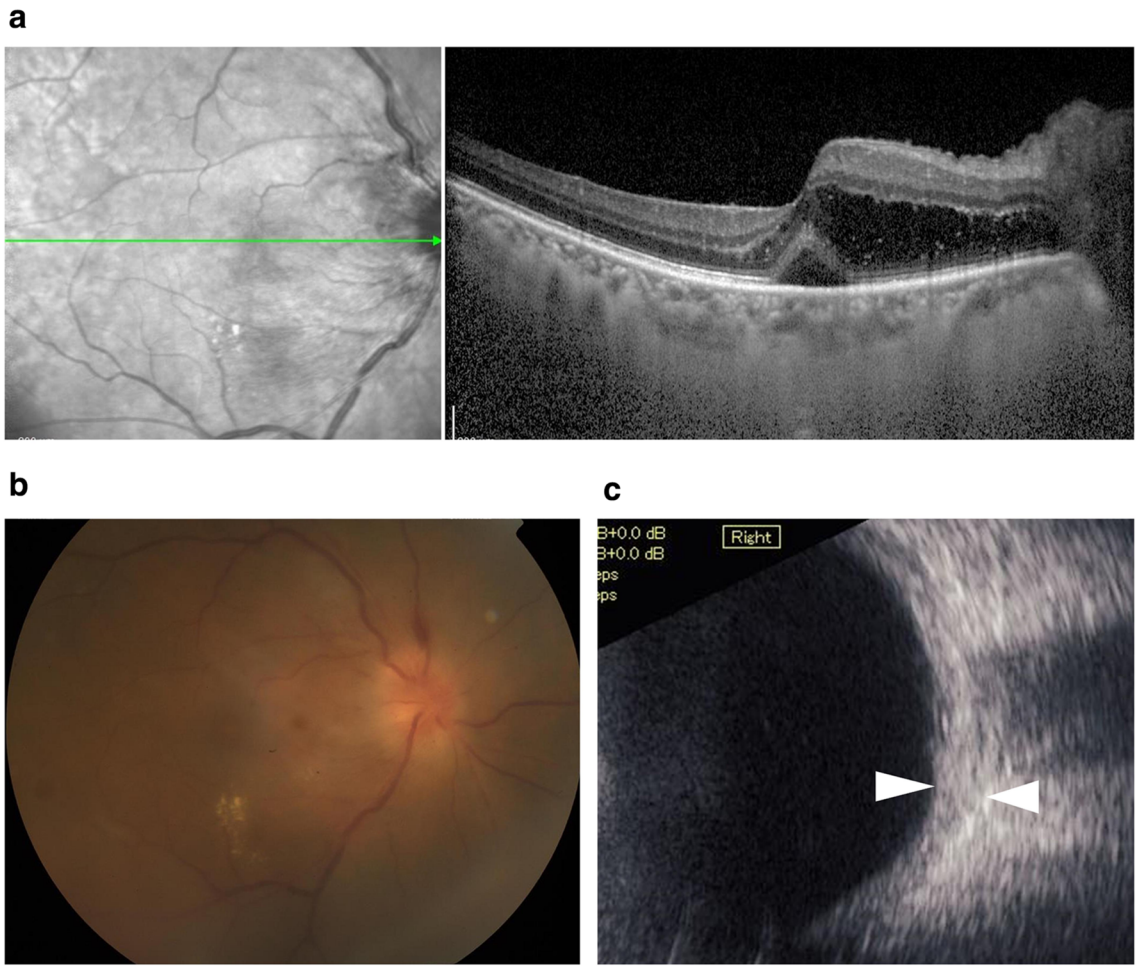

Fig. 1 Ocular findings of Patient 8 who developed posterior scleritis. **a** Optical coherence tomography showing cystoid macular oedema and serous retinal detachment. **b** Fundus photograph showing vitreous opacity and disc swelling. **c** B-mode ultrasonography showing the thickening of the posterior eye wall in the right eye

interval between initial ocular symptoms and subsequent systemic symptoms was 6.8 ± 8.3 (0–19) months. The systemic clinical features of the patients included auricular chondritis (Fig. 3) in ten patients (90.9%), inner ear disease in eight patients (72.7%), arthritis in five patients (45.5%), nasal chondritis in four patients (36.4%), respiratory tract chondritis (Fig. 2a) in two patients (18.2%), neurological symptoms in two patients (18.2%), cardiovascular symptoms in two patients (18.2%), and aortitis in one patient (9.1%). Six of the nine patients who underwent biopsy were histologically confirmed as having RP: five patients with inflammation of the auricular cartilage and one patient with the inflammation of the respiratory tract cartilage (Fig. 2b). The patients with respiratory chondritis developed airway narrowing (Patients 1 and 11), and Patient 1 underwent an urgent tracheotomy for respiratory failure. Regarding the neurological symptoms, one patient developed autoimmune encephalitis (Patient 8) and the other patient developed headaches, facial nerve palsy, and peripheral neuropathy (Patient 10). Patient 10 had myocardial infarction at 46 years of age.

Table 3 shows the treatments used. In terms of topical treatments, all the patients received corticosteroid eye drops. Two patients received subconjunctival steroid injections to treat scleral inflammation, and ten patients underwent systemic therapy involving immunomodulatory therapy or biological response modifiers. Further, ten patients received oral

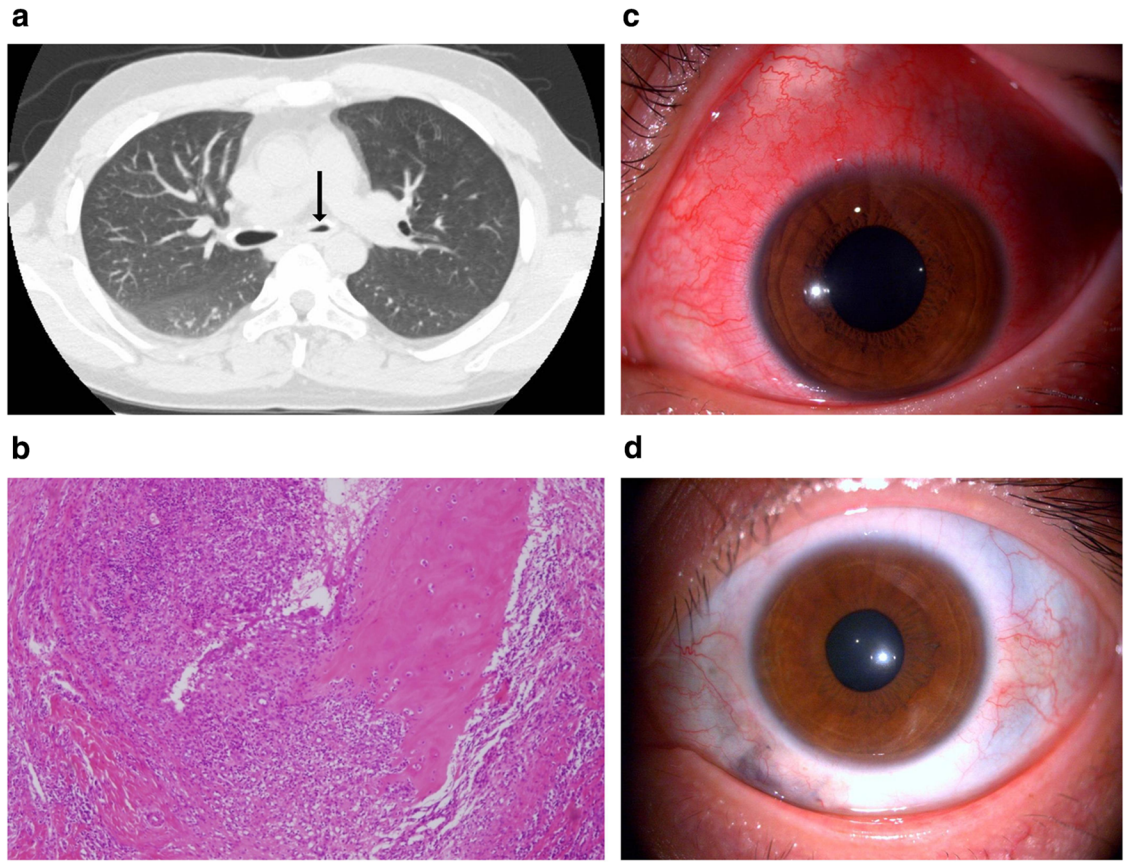

Fig. 2 Photographs of Patient 1. **a** Chest computed tomography showing narrowing (arrow) of the airway due to respiratory tract chondritis. **b** Respiratory tract biopsy shows the inflammation of the cartilage. **c** Diffuse scleritis of the left eye. **d** Recurrences of diffuse scleritis resulted in scleral thinning

corticosteroids, two received pulse steroid therapy, four received methotrexate, three received azathioprine, two received oral cyclosporine, and two received biological response modifiers. Systemic therapy was administered from the onset of ocular inflammation for 9.7 ± 11.7 months (range 0–28 months). Most of the systemic therapies were administered to treat systemic symptoms under the initiative of rheumatologists, dermatologists, and neurologists. After the administration of systemic treatment, the frequency of ocular inflammation relapse was 0.59 ± 0.61 per year (range 0–1.59 per year). Systemic steroid treatment was effective against both ocular inflammation and systemic symptoms in all ten patients who received them. Eight patients received oral prednisolone (> 5 mg/day) for systemic symptoms at their last visit; therefore, it is unclear which immunosuppressant was effective against ocular inflammation.

Discussion

RP is a rare but potentially lethal disease characterized by recurrent inflammation and destruction of cartilage. The overall mortality rate of people with RP is 9.0%, and respiratory failure and pulmonary infection are the leading causes of death in patients with this disease [3]. The most common systemic symptom of RP is auricular chondritis [3, 5, 20] and, in the present study, was observed in ten patients (90.9%) following ocular inflammation. Although Yang et al. [21] reported that the incidence of inner ear disease and arthritis among Chinese patients was lower than that among Caucasians, inner ear disease was observed in eight

Table 2 Systemic symptoms of each patient with ocular inflammation associated with RP

No.	Clinical features									Interval between initial ocular symptoms and subsequent systemic symptoms (month)
	Ocular inflammation	Auricular chondritis	Inner ear disease	Arthritis	Nasal chondritis	Respiratory tract chondritis	Neurological symptom	Cardiovascular symptom	Aortitis	
1	+[a]	−	+	−	+	+	−	+	−	15
2	+	+[a]	+	+	−	−	−	−	−	−
3	+	+	+[a]	−	−	−	−	−	−	−
4	+[a]	+	+	−	−	−	−	−	−	1
5	+[a]	+	−	−	−	−	−	−	−	0
6	+[a]	+	−	+	−	−	−	−	−	0
7	+	+	+	+[a]	−	−	−	−	+	−
8	+[a]	+	+	−	−	−	+	−	−	6
9	+	+[a]	+	+	+	−	−	−	−	−
10	+	+	−	−	+	−	+[a]	+	−	−
11	+[a]	+	+	+	+	+	−	−	−	19
Total	11/11 (100%)	10/11 (90.9%)	8/11 (72.7%)	5/11 (45.5%)	4/11 (36.4%)	2/11 (18.2%)	2/11 (18.2%)	2/11 (18.2%)	1/11 (9.1%)	6.8 ± 8.3

RP, relapsing polychondritis; +, present; −, absent

[a]Initial symptom

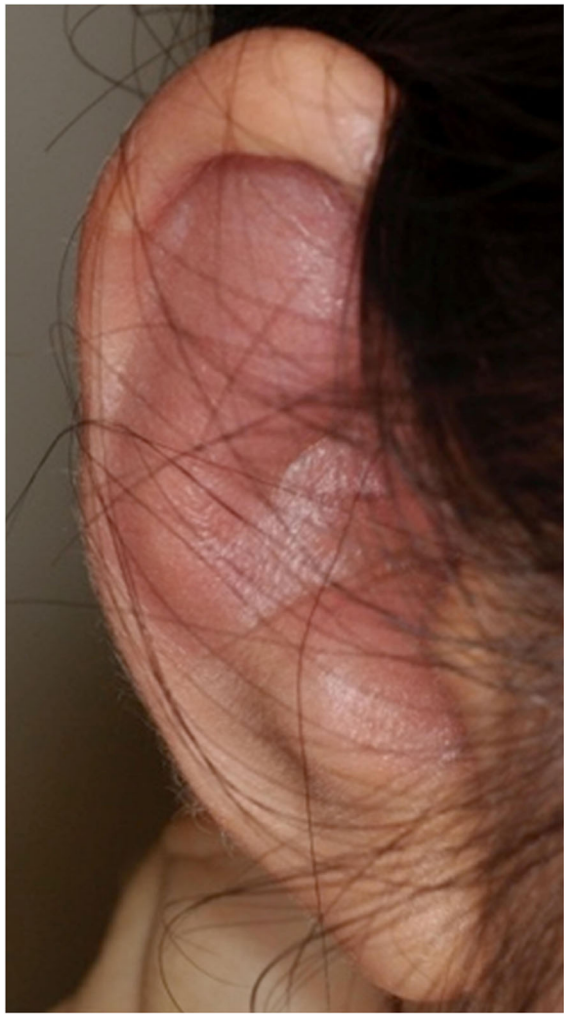

Fig. 3 Photographs of the right ear showing swelling and reddish auricles in Patient 5

patients (72.7%) and arthritis was observed in five patients (45.5%) in our study. Severe systemic symptoms, including respiratory chondritis, neurological symptoms, and cardiovascular symptoms, were also seen in several patients. Ocular inflammation was the first manifestation of RP in six cases. The interval between initial ocular symptoms and subsequent systemic symptoms was 6.8 ± 8.3 (0–19) months. Therefore, patients with symptoms such as painful swollen ear, impaired hearing, and arthritis (and especially patients with scleritis) should be carefully evaluated, and a rheumatologist should be consulted when appropriate. Moreover, patients with ocular inflammation must be closely followed up because some patients with RP develop systemic symptoms after a year. Prompt diagnosis and adequate treatment are necessary since RP can be a lethal disease.

In their study, Oka et al. [3] reported that 110 out of 239 Japanese patients with RP developed ocular symptoms during follow-up. Of the 110 patients, 62 had scleritis, 36 had conjunctivitis, and 26 had uveitis; however, they did not report any additional details. To the best of our knowledge, there have been four case reports (five patients) from Japan on RP-associated ocular inflammation that are written in English [13–16]. These reports identified the following types of ocular inflammation: diffuse scleritis (two cases), posterior scleritis (one case), episcleritis (one case), and panuveitis (one case). All the patients had bilateral involvement, and recurrent episodes were reported in three patients. A previous report from Europe and the USA that examined 13 patients showed that RP-associated scleritis is more often bilateral, necrotizing, recurrent, and related to decreased vision than scleritis associated with other systemic immune-mediated diseases [12]. They also showed that 69.2% of patients with scleritis and RP had one or more SIMD other than RP. [12] In contrast, only one patient (9.1%) with RP-associated ocular inflammation had SIMD, i.e. SLE, in our study. A previous study conducted in Japan reported that HLA-DRB1 * 16:02, HLA-DQB1 * 05:02, and HLA-B * 67:01 are associated with the susceptibility to RP. Moreover, they demonstrated that the representative susceptibility of HLA alleles to rheumatoid arthritis, SLE, Behçet disease, and Takayasu arteritis did not show enrichment in RP in Japanese population [22]. We performed HLA class I type in only one patient (Patient 8) and determined that she was positive for HLA-A24, A26, B35, and B59. The frequency of each HLA type differs from ethnicity to ethnicity and may lead to the presence or absence of comorbidities. In another report from China, the examination of 16 patients with RP-associated ocular inflammation showed bilateral involvement in 75% patients [21]. Of these 16 patients, ten had scleritis (nine with diffuse scleritis and one with nodular scleritis) and six had uveitis [21]. Similar to previous reports, all the patients in the present study showed bilateral involvement, and recurrent episodes were observed in 91% of our patients. Similar to the report from China [21], none of the patients in the present study had necrotizing scleritis, and diffuse scleritis was most frequently seen in the present study. According to previous reports, uveitis occurs less

Table 3 Treatments of patients with ocular inflammation associated with RP

No.	Topical treatment		Systemic treatment							
	Steroid eye drops	Subconjunctival injection of steroid	Oral NSAIDs	Oral steroid	Steroid pulse therapy	Methotrexate	Azathioprine	Cyclosporine	Biologics	Systemic treatment at last visit
1	+	+	−	+	+	+	+	+	+ (IFX → ETN → TCZ)	PSL 10 mg +TCZ+MTX
2	+	−	−	−	−	−	−	−	−	−
3	+	+	+	+	−	−	−	−	−	PSL 4 mg
4	+	−	−	+	−	−	−	−	−	PSL 8 mg
5	+	−	+	+	−	−	−	−	−	mPSL 3 mg
6	+	−	−	+	−	+	−	−	−	PSL 20 mg
7	+	−	+	+	−	+	−	−	−	PSL 7 mg+MTX
8	+	−	+	+	+	−	−	−	−	PSL 17.5 mg
9	+	−	−	+	−	−	−	−	−	PSL 12.5 mg
10	+	−	−	+	−	−	+	+	+ (ABT)	PSL 18 mg +ABT+AZA
11	+	−	−	+	−	+	+	−	−	PSL 14 mg+MTX
Total	11/11 (100%)	2/11 (18.2%)	4/11 (36.4%)	10/11 (90.9%)	2/11 (18.2%)	4/11 (36.4%)	3/11 (27.3%)	2/11 (18.2%)	2/11 (18.2%)	

RP relapsing polychondritis, *NSAIDS* non-steroid anti-inflammatory drugs, + present, − absent, *IFX* infliximab, *ETN* etanercept, *TCZ* tocilizumab, *ABT* abatacept, *PSL* prednisolone, *MTX* methotrexate, *AZA* azathioprine

frequently than scleritis in RP [3, 5]. There have been some reported cases of panuveitis [15, 21, 23–26] or hypopyon uveitis [21, 27–29] associated with RP. Two patients in the present study had anterior uveitis without hypopyon. During follow-up, one of the patients with anterior uveitis also had mild disc swelling in the right eye (Patient 10). Fluorescence angiography showed hyperfluorescence of the bilateral optic discs; however, vasculitis was not observed. At the time, his visual acuity was 6/6 in both eyes, and the reason for the disc swelling was thought to be anterior chamber inflammation, which resolved after treatment with oral steroids. No patients suffered from conjunctivitis in the present study, and this may be because mild cases of ocular inflammation were not referred to our hospital.

The visual prognosis was good in the present study, and at their final visit, none of the patients had decreased vision due to RP. This result differs from that of a previous study on Caucasians that visual prognosis is poor compared with other systemic immune-mediated diseases [12]. They reported two patients who developed first episodes of scleritis and RP, while they were on biological response modifiers for treating ankylosing spondylitis and uveitis. These two patients repeated recurrent episodes of scleritis and RP while on several biological response modifiers, and one of the patients exacerbated to light perception in both the eyes. In these aforementioned patients, comorbid HLA-B27+ ankylosing spondylitis might have contributed to the recurrent episodes of scleritis and RP. In our study, only one patient who had comorbid SIMD (SLE) did not develop SLE retinopathy. Most of our patients had no other SIMDs, and it may be one of the causes of good visual prognosis. Our result also differs from that of a previous study conducted in China, in which female patients had milder inflammation and a better visual prognosis than male patients [21]. In our study, the sex of the patient did not influence visual prognosis.

We found decreased vision in Patient 8 due to posterior scleritis (before systemic treatment was administered); however, her vision improved immediately after pulse steroid therapy. Patient 7 also presented with posterior scleritis, although his vision did not decrease over their follow-up. There are three possible explanations for the good visual prognosis in our study. First, the immediate initiation of systemic therapy prevented the development of ocular inflammation; seven patients were administered systemic therapy within 7 months from ocular inflammation onset (Table 1). Second, intensive immunosuppressive therapy for systemic symptoms contributed to maintaining the inactivity of the ocular inflammation. Third, the types of ocular inflammation found in this study were not very severe.

Sainz-de-la-Maza et al. [12] suggested that immunomodulatory therapy or biological response modifiers are appropriate treatments for patients with RP and scleritis. Additionally, several reports demonstrated the efficacy of immunomodulatory therapy [30, 31] and biological response modifiers [14, 32, 33]. In the present study, Patients 1 and 10 were treated with both biological response modifiers and immunomodulatory therapy for severe systemic symptoms. It is difficult to determine whether biological response modifiers or immunomodulatory therapy is effective treatments for RP-associated ocular inflammation because most of our patients were also treated with high-dose prednisolone. The rarity of RP and the necessity of treating systemic symptoms make it difficult to determine which systemic treatment was the main contributing therapy against RP-associated ocular inflammation.

This study has several limitations. First, the selection process was not independent of bias because of the retrospective design. Second, the number of patients was small because this study was conducted at one university hospital and because the disease itself is very rare. Despite these limitations, we believe that these results provide important insights into the clinical characteristics and complications of Japanese patients with RP-associated ocular inflammation.

In our study, RP-associated ocular inflammation was often bilateral, with recurrent episodes, as previously reported. Diffuse scleritis was the most common type of ocular inflammation in our study, and we frequently observed systemic symptoms such as auricular chondritis, inner ear disease, and arthritis. Some patients also developed severe systemic symptoms, including respiratory failure, autoimmune encephalitis, and myocardial infarction. Therefore, it is important to carefully question patients with ocular inflammation regarding painful swollen ear, painful joints, and impaired hearing. Early diagnosis, appropriate and prompt treatment, and collaboration with rheumatologists are vital to optimize health and visual prognosis in these patients.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

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