

age distribution of disease onset is indicated in Fig. 1. The average age at onset was 52.7 years with a range from 3 to 97 and the average disease duration was 5.3 years with a range from 1 to 33. The ratios of patients whose disease duration was shorter than 2 and 5 years were 25 and 65 % of whole patients, respectively. We suggested that the time to diagnosis was not so long because a large part of patients had relatively short duration of disease. Older people (more than 51 years old) tend to develop RP rather than younger people (0-20 years old).

Clinical features

Initial lesions and symptoms in patients with RP varied considerably. Auricular chondritis was shown in 137 patients (57.3%) and is the earliest and most frequent manifestation. 41 patients (17.2%) developed respiratory symptoms as an initial manifestation which included hoarseness, persistent cough, dyspnea, wheezing and inspiratory stridor caused by the inflammation of laryngeal, tracheal and bronchial cartilages.

Ocular symptoms (22 patients, 9.2%), arthritis (15 patients, 6.2%), inner ear disorder (9 patients, 3.8%), neurological symptoms (7 patients, 2.9%) and nasal chondritis (5 patients, 2.1%) were recognized in relatively small numbers of patients at the onset of disease.

The prevalence and severity of the disease symptoms increased during follow-up (Table 2).

Ninety-seven patients (40.6%), 47 patients (19.7%) and 119 patients (49.8%) showed tracheal lesion, laryngeal lesion and laryngotracheal involvement, respectively. Forty-nine patients (20.5%) suffered from upper airway collapse and 42 patients (17.6%) required tracheotomy. 22 patients (9.2%) underwent stent placement and 12

patients (5.0%) received nasal continuous positive airway pressure because of their tracheobronchomalacia.

Auricular and nasal chondritis were seen in 187 patients (78.2%) and 94 patients (39.3%), respectively. Saddle nose deformity after the nasal chondritis was observed in 76 patients (31.8%).

Otitis media complications with vestibular dysfunction were observed in 64 patients (26.8%). Prolonged inflammation in inner ear and vasculitis of internal auditory artery²⁾ caused hearing loss (52 patients, 21.8%) and the vestibular dysfunction (39 patients, 16.3%) such as dizziness, ataxia, nausea and vomiting.

Joint, skin and eye involvement were observed in 92 (38.5%), 32 (13.4%), and 109 (45.6%) patients, respectively. The arthritis was mainly asymmetric, migratory and non-erosive.

Dermatologic manifestations included the purpura, papules, macules, vesicles, bullae, chronic dermatitis and nodules. Ocular symptoms included recurrent episcleritis, conjunctivitis, keratitis, uveitis, proptosis, periorbital edema, tarsitis and extra-ocular muscle palsy.

Neurologic and renal involvements were observed in 23 patients (9.6%) and 16 patients (6.7%), respectively. Cardiovascular involvement, including aortic insufficiency, myocarditis, pericarditis, paroxysmal atrial tachycardia, heart block and vasculitis, was observed in 17 patients (7.1%).

Laboratory findings

Most of patients with RP showed the elevation of erythrocyte sedimentation rate (ESR, 68.2%) and C-reactive protein (CRP, 86.2%). Urinalysis was usually normal. Although the data were not routinely available, matrix metalloprotease (MMP)-3 and antibody to

type II collagen were found in 20.1% and 13.8% of patients, respectively.

Conventional radiograph showed changes in larynx, trachea, surrounding soft tissues and bronchi. In two cases, respiratory tract involvement was assessed by laryngoscopy. Endobronchial ultrasonography revealed fragmentation and edema of tracheobronchial cartilage in two patients¹¹⁾. 3 dimensional-CT scan was performed in 61 patients (25.5%) and conventional CT was conducted in 30 patients (12.6%).

Biopsies were performed in 228 patients (95.4%) and 138 patients (60.5% of patients who underwent biopsy) were diagnosed with histological confirmation of RP.

Treatments

Main treatment for RP patients even with airway involvement remains medical management. In the medication history profile, non-steroidal anti-inflammatory drugs were administered alone for 8 patients (3.3%) who had mild auricular or nasal chondritis. 219 patients (91.6%) had received at least one course of prednisolone through oral administration (204 patients, 85.4% of all patients), intravenous infusion (17 patients, 7.1%) and pulse therapy (40 patients, 16.7%). Low daily dose of prednisolone was administered in the majority of patients. Minocycline hydrochloride was used in 8 patients with RP but its effect remained unclear.

Immunosuppressants which were used against the chronic progression of RP included methotrexate (MTX, n=47), cyclophosphamide (CPA, n=30), cyclosporin A (CYA, n=20) and azathioprine (AZP, n=22). MTX, CPA, and CYA elicited considerable effects on clinical outcomes in 64.0%, 66.7%, and 73.7% of patients, respectively. MTX was added as an adjuvant treatment in refractory RP patients who required higher maintenance doses of prednisolone to reduce the overall steroid requirement. 3 patients were maintained with MTX alone. AZP was less effective than other agents and the rate

was estimated as fewer than 40%. Tacrolims was used in 3 patients and ameliorated manifestations in one patient.

Of those 47 patients with the combined therapy of steroid with MTX, 20 patients (42.6%) had some respiratory symptoms and did not require any surgical intervention (Fig. 2). In contrast, all 12 patients (5.0% of all patients) treated with prednisolone alone underwent tracheotomy. CPA, CYA and AZP treatment in conjunction with steroid administration also reduced the prevalence of airway involvement in patients with RP (54.5%, 50.0% and 57.0%, respectively, Fig. 2).

Discovery of the central role of tumor necrosis factor (TNF)- α and interleukin (IL)-6 in autoimmune/inflammatory diseases and subsequent development of anti-cytokine agents have quickly led to the clinical application of them in treatment of refractory RP.

In our survey, infliximab, an anti-TNF- α agent, treatment resulted in a response in 6 cases of 10 RP patients with airway involvement that had not responded to conventional immunosuppressants. Etanercept (anti-TNF- α) and tocilizumab (anti-IL-6) treatment also showed a sustained response in 1 case of 3 patients with refractory RP.

Prognosis

We summarized the prognostic outcome of patients of RP in our cohort in Fig. 3. Medication was discontinued without any manifestation in 11 patients (4.6%). All these patients exhibited auricular chondritis without respiratory involvement and 2 of the patients had scleritis.

One hundred and fifty-nine patients (66.5%) were well controlled and, in total, 71.1% of patients in our cohort responded to the treatments. 32 patients (13.4%) showed limited response and 9 patients (3.8%) suffered from progressive disease or relapse. 22

patients (9.0%) died and the causes of death were as follows; respiratory failure (8 patients), pulmonary infection (4), cardiovascular disease (2), cerebrovascular disease (2), suicide (1), myelodysplasia (1), leukemia (1) and unknown reason (2).

Discussion

We conducted a large-scale survey of patients with RP in Japan. Surveyed physicians dispersed widely on geographic location and a large part of survey responses were limited in patient number even in the main surveys. Considering the survey response rate and the number of collected patient data, the RP prevalence in Japan was estimated to be similar to that in the United States⁵⁾.

The disease severity and prognosis of RP largely depends on airway and cardiovascular involvement¹⁰⁾. It has been reported that airway involvement were seen in approximately half of all RP patients during follow-up, while the manifestation were observed in only 20% of the patients at the onset of disease^{12, 13)}. 10-30% of patients with airway involvement were treated with tracheotomy and the leading cause of death was airway collapse and/or pulmonary infection¹²⁻¹⁴⁾. These study results were similar to those in our study (Table 2, Fig. 3). Several studies reported a female predominance in RP patients with airway involvement (male-female ratio, 1:2.3-2.8)^{12, 13)} but the ratio in our study was approximately 1:1.

It was suggested that the detection of tracheal wall thickness in CT scan was remarkably effective to the diagnosis of airway involvement in patients with RP and dynamic expiratory CT scan was more useful to indicate the lesions than conventional CT scan^{12, 15-18)}. Despite of the advances in CT scanning techniques, bronchoscopy is essential for the diagnosis because it identify additional findings in approximately 25% of RP patients who received the CT scan¹²⁾. Miyazawa et al. described the

endobronchial ultrasonography was useful to indicate fragmentation and edema of cartilage in patients with RP¹¹⁾.

It has been reported that cardiac involvement were seen in 15-46% RP patients and the second cause of RP death^{10, 19)}. The male-to-female ratio was high (1:0.4) in RP patients with cardiac complications²⁰⁾. A retrospective chart review of 33 RP patients with cardiac surgery recommended that ultrafast chest computed tomography, magnetic resonance imaging or trans-esophageal echocardiography should be repeated every 6 months because subclinical development of cardiovascular involvement was occasionally observed in RP patients²⁰⁾.

Certainly, several reports have described the latent phase of cardiovascular complications for a few years after the onset of RP in relatively young patients²¹⁻²⁴⁾. Several RP patients developed febrile vasculitis after RP onset with or without anti-neutrophil cytoplasmic antibody (ANCA)²⁵⁻³⁰⁾. The activity of the vasculitis correlated well with severity of scleritis in patients with RP^{2, 31, 32)}.

In our study, we found that cardiovascular involvement was less frequent in Japan (7.1 %) as compared with other reports^{10, 19)}. The reason for the low prevalence of cardiovascular disease remains unclear. Low prevalence of cardiac complications was reported in Japanese patients with rheumatoid arthritis as well³³⁾. We speculate that this is a public health issue of Japanese people regardless of the presence or absence of diseases.

No specific laboratory diagnostic test exists for RP and the diagnosis is made by clinical features and pathological findings of chondritis²⁸⁾. Typical pathological changes began with the loss of proteoglycans' basophilic staining of cartilage. Then lymphocytes, plasma cells and neutrophils infiltrated into perichondrial area,

degenerated and decreased the number of chondrocytes. Finally, the cartilage was replaced by fibrous tissue³⁴⁾.

In this study, tissue biopsies were conducted in 95.4% of patients with RP and a definitive diagnosis was obtained in 60.5% of patients who underwent biopsy. To reach accurate diagnosis of RP, it was essential that physicians perform a deep biopsy to obtain the chondral tissue in the site with acute inflammation²⁸⁾.

In laboratory experiments of biopsy specimen, immunoglobulin and C3 component of complement deposited to margin of cartilage and perichondrial vessel wall³⁴⁾. Antibody to type II collagen was detected in patients with RP from the disease onset and the titers were correlated with disease activity³⁵⁾. Hyper-activation of macrophage/monocytes in peripheral blood of RP patients was reported using cytokine profile analysis³⁶⁾.

We found that serum level of soluble triggering receptor expressed on myeloid cells 1 (TREM1), an inflammatory receptor on macrophage/monocytes, was correlated with disease activity³⁷⁾. These data suggest that over-activation of immune system in the whole organism of RP patients converge on the chondritis of RP in a polyphyletic manner.

Several studies reported the possibility that combination therapy with prednisolone and immunosuppressants was effective for patients with RP^{21, 38, 39)}, especially that with methotrexate^{1, 2, 40, 41)}. In agreement with the studies, our survey revealed high prevalence of airway involvement in patients with prednisolone monotherapy and relatively low prevalence of the involvement in patients with the combination therapy. We recommend use of the combination therapy using prednisolone and immunosuppressants in RP patients with airway involvement.

We found several case reports showed the effectiveness of anti-cytokine antibodies, such as infliximab⁴²⁾, adalimumab⁴³⁾, anakinra^{44, 45)} and abatacept⁴⁶⁾. We presume that the biological agents are applicable for patients with refractory RP based on the results of this survey. However, it is important to control infections of respiratory tracts before administrating such biological agents.

Endoscopic and surgical interventions are sometimes unavoidable for respiratory distress and such interventions with experienced clinicians were effective for the treatment of airway involvement in patients with RP^{12, 47)}. The progression of airway involvement occurs even under intensive medication and intervention in some patients with RP and a new modality is awaited for treating such patients. We are currently planning to conduct a prospective study using a patient conducted patient registry system which allows us to collect detailed status data of patients.

Conclusions

We described here patient profiles and major clinical features in patients with RP in Japan. Airway involvement of RP was fundamentally progressive and required frequent clinical checks and appropriate medications. Combination therapy with prednisolone and immunosuppressants may be beneficial for controlling airway involvement of RP than prednisolone monotherapy.

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Disclosure

All authors have no conflict of interest.

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Figure legends

Fig. 1 Age distribution of disease onset in patients with RP

The mean age at onset of disease was 52.7 years old with a range from 3 to 97 years old. Older people (more than 51 years old) tend to develop RP rather than younger people (0-20 years old).

Fig. 2 Effects of immunosuppressants to the airway involvement of RP patients

Prevalence rates of airway involvement in patients with RP were 100, 42.6, 50.0 and 57.0% in treatment with steroid only, steroid with MTX, CPA, CYA and AZP, respectively, with and/or after each treatment.

Fig. 3 Summary of prognostic outcome in patients with RP in this survey

Medication was discontinued without any manifestation in 11 patients (4.6%). 159 patients (66.5%) were well controlled and, in total, 71.1% of patients in our cohort responded to the treatments. 32 patients (13.4%) showed limited response and 9 patients (3.8%) suffered from progressive disease or relapse. 22 patients (9.0%) died.

Table 1 Summary of Japan RP Questionnaire

a. Patients' profile

Sex, onset age, follow-up years and diagnostic delay

b. Clinical features

Primary and follow-up

c. Laboratory findings

Laboratory tests, image analysis and histopathologic features

d. Treatment

Non-steroidal anti-inflammatory, prednisolone, immunosuppressants, antibiotics and surgical intervention

e. Prognosis and complications

Tracheal collapse, tracheotomy, vulvar surgery and death

Table 2 Characteristics of patients with RP in McAdam series¹⁰⁾ and current survey

	McAdam (n=159)		Current survey (n=239)	
Profile				
Male-female ratio	83:76		127:112	
Mean age			57 (range 6-104)	
Mean age of disease onset	44		53 (range 3-97)	
Disease duration (yr)			5.3 (range 1-33)	
Clinical features (%)				
	McAdam		Current survey	
	Onset	Follow-up	Onset	Follow-up
External ear	26	89	57	78
Internal ear	6.4	46	3.8	27
Nasal cartilage	13	72	2.1	39
Airway	14	56	17	50
laryngo				20
tracheobronchial				41
Eye	14	65	9.2	46
conjunctivitis				15
scleritis				26
uveitis				11
Arthritis	23	81	6.2	39
Skin		17		13
Cardiovascular		24		7.1

Neurological	2.9	9.6
Renal		6.7
Myelodysplasia		1.7

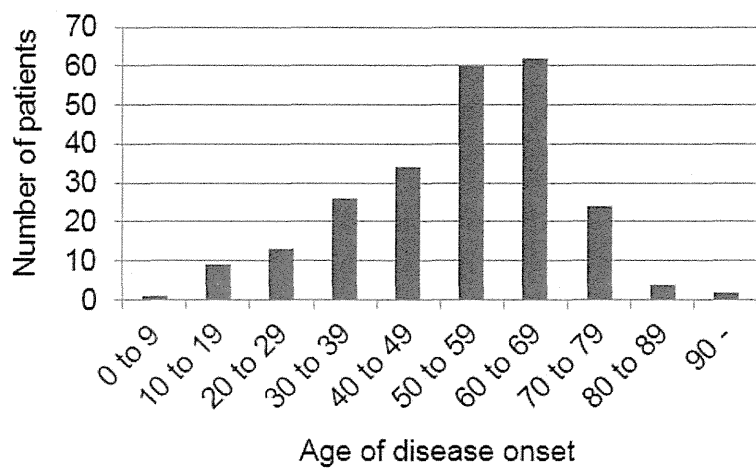


Fig. 1