

**Nationwide Epidemiologic Study of Relapsing Polychondritis in Japan;
results of 239 cases**

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Running title: Epidemiology of Relapsing Polychondritis in Japan

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ABSTRACT

Objective: Reveal the nationwide epidemiological information about relapsing polychondritis (RP) in Japan.

Methods: A questionnaire was sent throughout Japan to the medical doctors who have experienced the practice of RP patients. The questionnaire includes patient profiles, clinical manifestations, examinations for diagnosis, therapeutic regimen, treatment response, and prognosis.

Results: The averaged age at the time of diagnosis was 52.7 years old, with a range from 3 to 97 years old. The male-to-female ratio was almost equal. In laboratory findings, most of patients showed the elevation of C-reactive protein (84.5%) or erythrocyte sedimentation rate (68.5%), and

in some cases, the elevations of matrix metalloprotease (MMP)-3 and antibody to type II collagen were found. However, some patients showed no elevation of these parameters with insidiously advancing fibrosis. In this cohort, airway involvement was observed in 49.8%, and was strongly associated with the poor prognosis. Therapeutic regimen demonstrated the usage of prednisolone in 92% of the patients, and in some cases, additional immunosuppressive agents were used. The response rate to these agents was; 64% to methotrexate, 66% to cyclophosphamide, 74% to cyclosporine, and 38% to azathioprine. While 71.1% of total RP patients responded to therapy in some extent, 17.2% of patients showed no response, and

9.0 % of patients were dead. The cause of death was mainly associated with respiratory involvement.

Conclusions: This is the first nationwide epidemiologic survey of RP. There was no gender-, geographic-specific distribution. The incidence of airway involvement was strongly associated with the poor prognosis.

Word count: 245

INTRODUCTION

Relapsing polychondritis (RP) is an uncommon inflammatory disorder of unknown etiology characterized by an episodic and generally progressive course affecting predominantly the cartilage of the ear, nose, peripheral joints, and respiratory tract (1-4). Inflammation of other tissues such as the eyes, heart, blood vessels, inner ear, and kidneys may also be present (1-4). When the visceral is affected by inflammation, RP is a potentially lethal disease.

The epidemiological studies of this disease have been mainly done in Caucasian population (4). The incidence of RP in Rochester, Minnesota is estimated to be 3.5 cases per million populations per year (5). It seems to occur with equal frequency in all racial groups, but there are very few data available on non-Caucasian populations. Several cases of this disease have been reported from South India (6), North India (7), and Singapore (8). However, there have been no reports of nationwide surveillance of this disease both in Caucasians and in non-Caucasians.

Furthermore, the choice of therapy for this disease is largely empiric, because there is little information about the natural history of RP and its response to therapy because its rarity and the lack of long-term follow up.

Here, we conducted the nationwide study about the epidemiology of RP in Japan, and present the clinical course, clinical manifestations, treatment, and the response to therapies of 239 patients with RP.

MATERIALS AND METHODS

A two-stage questionnaire survey on RP patients was conducted. Using the questionnaires, we asked about beliefs and practices regarding RP management. In September 2009, we initially sent out the first stage simple letter (totally 1894 letters) to ask whether they experienced RP patients diagnosed according to Damiani's criteria (9) for these ten years. The second stage, to the hospitals with an experience of medical management of RP patients, a questionnaire was mailed to the 395 professionally active physicians who belong to the departments in charge of RP, at Japanese national, public and private universities, public or private hospital in Japan. The questionnaire was to be answered anonymously. This questionnaire survey was approved by the ethics committee of St. Marianna University School of Medicine.

The questionnaire consisted of 5 questions, of which questions 1 and 2 were related to patient profiles and clinical features, question 3 to examinations for diagnosis, questions 4 to treatments, and

question 5 to prognosis and complications (Table 1). Concerning epidemiology, question 1 was asked about the age at onset of the disease, sex, and duration of follow-up. Question 2 concerned the first and consequent symptoms in patients with RP. Question 3 concerned the diagnostic examinations; laboratory features, diagnostic imaging and histological analysis. Question 4 was related to the selection of treatments and also asked whether the selected treatments were useful or not based on the physician's evaluation. Question 5 was asked about the prognosis and complications.

A total of 121 questionnaires were returned (30.6 % response rate) and 239 (127 males, 112 females) of the respondents had been diagnosed with RP by a professionally physician. These 239 patients were evaluated in the study.

RESULTS

Age and symptom at onset of the disease.

Of the 1894 hospitals to which the first stage letter were sent, 856 hospitals (45.2%) responded. Next, we sent the second stage letter of questionnaire to 395 hospitals; of those, 121 (30.5%) reported one or more patients with RP.

The total number of RP patients reported in this survey was 239 (127 males, 112 females; male-to-female ratio was 1.13:1). The mean age at onset of disease was 52.7 years old, with a range from 3 to 97 years old. The distribution of age at onset of symptoms is shown in Figure 1. The onset of disease occurred in 4.2 % of

patients at an age younger than 20 years old, in 31.0 % of patients between the ages of 21 and 50 years old, and in 63.6 % of patients at an age older than 50 years old. The most common age at onset of RP was 50 –69 years old.

Investigations for diagnosis.

Laboratory findings were non-specific. Most of patients with RP showed the elevation of erythrocyte sedimentation rate (ESR) in 163 patients (68.5%) and C-reactive protein (CRP) in 206 patients (84.5%), consistent with acute or chronic inflammation. Urinalysis was usually normal. Although not routinely available, matrix metalloprotease (MMP)-3 and antibody to type II collagen were found in 48 and 33 cases, respectively.

Conventional radiograph showed changes in the larynx, trachea and surrounding soft tissues as well as the bronchi of the lung. In two cases, respiratory tract involvement was assessed by laryngoscopy. Endobronchial ultrasonography revealed changes such as fragmentation and edema in the tracheobronchial cartilage in these two patients. CT scan was conducted in 91 cases (38.1%) out of 239 cases. Three dimensional-CT scan, which contributes to elucidate stenotic bronchial lesion, was performed in 61 cases, and conventional CT was in 30 cases.

Biopsy from ear cartilage or other inflamed areas was performed in 228 cases (95.4%) of 239 patients in this survey, and 138 patients were diagnosed with histological confirmation and other cases

met Damiani's criteria.

Clinical features.

Of the 239 patients with RP, initial lesions and symptoms were as follows; auricular chondritis (137 patients: 57.3%), respiratory symptoms (41 patients: 17.2%) such as cough, hoarseness, difficulty of breathing, eye involvement (22 patients) such as scleritis, uveitis, arthritis (15 patients), inner ear symptoms (9 patients) such as dizziness, difficulty in hearing, neurological symptoms (7 patients) such as headache and meningitis, nasal chondritis (5 patients), and so on.

The clinical feature observed in the whole course of disease was summarized in Table 2. 187 patients (78.2%) had auricular chondritis. The pain, red or violaceous dislocation, swelling and tenderness of the cartilagiou portion and the non-cartilaginous lobe were present in almost all patients with auricular chondritis.

The nasal chondritis was seen in 94 patients (39.3%) of 239 RP patients. It presented with nasal pain, redness and swelling, nasal stuffiness, rhinorrhea or epistaxis. The saddle nose deformity by the destruction and collapse of the nasal bridge was observed in 76 patients (31.8%) of patients with nasal chondritis.

The vestibular dysfunction was observed in 64 patients (26.8%) in this survey. They showed the reduced hearing (52 patients: 21.8%) and the vestibular dysfunction (39 patients: 16.3%) with dizziness, ataxia, nausea and vomiting, which were caused by inflammation of the

middle ear and audiovestibular structures and/or vasculitis of the internal auditory artery.

119 patients (49.8%) had laryngotracheal involvement [tracheal lesion: 97 patients (40.6%), laryngeal lesion: 47 patients (19.7%)]. The respiratory symptoms by the inflammation of the laryngeal, tracheal and bronchial cartilages included the hoarseness, persistent cough, dyspnea, wheezing and inspiratory stridor. 49 patients (20.5%) with respiratory symptoms showed the upper airway collapse caused by the damage to the laryngeal and epiglottal cartilage and required the tracheotomy (42 patients: 17.6%), management with stents (22 patients: 9.2%) or nasal continuous positive airway pressure such as bilevel positive airway pressure (12 patients: 5.0%).

Non-erosive arthritis, skin involvement and eye involvement were observed in 92 (38.5%), 32 (13.4%), and 109 (45.6%) patients, respectively. Most of arthritis in this survey was asymmetric, migratory, seronegative and non-erosive joint symptom. Dermatologic manifestations included the purpura, papules, macules, vesicles, bullae, chronic dermatitis, or nodules on the limbs. The eye involvement included recurrent episcleritis, conjunctivitis, keratitis, or uveitis. Additional eye manifestations involved proptosis, periorbital edema, tarsitis and extraocular muscle palsy.

Neurological and renal involvements in this survey 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%) of the 239 patients.

Treatments

Treatment has been symptomatic in this disease. Non-steroidal anti-inflammatory drugs (NSAIDs) alone were adequate for 8 patients with mild auricular or nasal chondritis.

More serious symptoms required the corticosteroids. Most patients (219 patients, 91.6%) had been, at least once, treated with corticosteroids during a period of the disease (oral steroid: 204 cases, intravenous therapy: 17 cases, pulse therapy: 40 cases). Most patients require a low daily dose of prednisolone for maintenance. Minocycline hydrochloride was used in 8 patients with RP but obvious effects were not noted

Immunosuppressant used to control symptoms and progression of the disease, include azathioprine (AZP), methotrexate (MTX), cyclophosphamide (CPA), and cyclosporin A (CYA). As shown in Table 3, MTX, CPA, and CYA elicited considerable effects on RP progression. Effective rate of MTX, CPA, and CYA was 64.0%, 66.7%, and 73.7%, respectively. AZP, which effective rate was 37.6%, was less effective than these agents. Tacrolims was used in only 3 patients, and one of these patient showed responses.

In 47 refractory RP patients who require higher maintenance doses of prednisolone, MTX was administered as an adjuvant treatment. MTX was used with prednisolone

to reduce the overall steroid requirement for disease control; however, 3 patients may eventually be maintained with MTX alone. Of 47 patients with the combined therapy of steroid with MTX, 20 patients (20/47 patients, 42.6%) had some respiratory symptoms. In contrast, all patients treated with steroids alone showed serious airway involvements. CPA or CYA treatment in conjunction with steroid administration showed a reduction of airway involvement (54.5% and 50.0%, respectively) while controlling symptoms (Figure 2).

Recent advances in understanding of the pathological basis of inflammatory diseases have led to the development of biological therapies. The discovery of the central role of tumor necrosis factor (TNF)- α and interleukin (IL)-6 in autoimmune diseases such as rheumatoid arthritis, and the subsequent introduction of the anti-TNF- α agents infliximab and etanercept, or the anti-IL-6 agent tocilizumab, have transformed the treatment of refractory RA.

In our survey, biological therapies were performed in a few cases with refractory disease. Infliximab treatment resulted in a response in 6 cases of 10 RP patients with airway involvement that had not responded to conventional immunosuppressant (effective rate, 60.0 %). Etanercept or tocilizumab treatment also showed a sustained response in 1 case of 3 patients with refractory RP. Although biologics seemed to be potential therapeutic agents, very few cases reported in this survey were not sufficient to assess the efficacy and

toxicity of these agents in RP.

Prognosis

We summarized the overall prognosis of our cohort (Figure 3). 11 patients (4.6%) cured. All these cured patients had auricular chondritis, 2 of them had scleritis, though they had no respiratory involvement. Furthermore, 159 patients (66.5%) were improved by the treatment. Thus in total, 71.1% of our cohort responded to the treatment in some extent. However, 32 patients (13.4%) showed no response to the treatment, 9 patients (3.8%) had become worse, and notably, 22 patients (9.0%) were died. The cause of death are as follows; respiratory failure (8 patients), pulmonary infection (4 patients), cardiovascular disease (2 patients), cerebrovascular disease (2 patients), and suicide (1 patient), myelodysplastic syndrome (MDS; 1 patient), leukemia (1 patient), unknowun (2 patients).

DISCUSSION

RP is known as an uncommon disorder of unknown etiology. There have been no reports of nationwide surveillance of this disease both in Caucasians and in non-Caucasians. This study is the first nationwide epidemiologic survey of RP. Epidemiological studies of this disease have been mainly done in Caucasian population (4). Although several cases of this disease have been reported from South India (6), North India (7), and Singapore (8), there are very few data available on non-Caucasian populations. Therefore, this disease has been sometimes considered to predominantly

affect Caucasian population (1). However, this study demonstrates that at least more than 200 patients with RP exist in Japan, and the clinical feature such as age of disease onset (Fig.1) and clinical manifestations (Table.2) of this disease in Japanese patients were similar with those of Caucasians (1-4). These results suggest that RP may occur with almost equal frequency between Caucasians and Asian populations. In the future study, it will be important to determine the precise incidence of this disease in Japan, which is very difficult because this disease is rare, still uncommon, and sometimes difficult to make a diagnosis.

This study also revealed that the diagnosis of RP was mainly made based on a diagnostic criterion by Damiani (9, 10), because no specific laboratory tests exist (1-4, 11). Histological findings of biopsied specimen are known to strengthen the diagnosis (12). Typical pathologic change was begun with the loss of proteoglycans' basophilic staining of cartilage. Then lymphocytes, plasma cells and neutrophils infiltrated perichondrial area, degenerated chondrocytes and decreased the number of them. Finally, the cartilage was replaced by fibrous tissue (12). Indeed, in this study histological examination of biopsied specimen was conducted in 228 cases out of 239 cases (95.4%), suggesting that many of Japanese physician have tried to confirm the diagnosis with histological findings. Typical pathological findings were present in 138 cases out of 228 cases of histological examination. However, 90 cases were difficult to make a firm diagnosis of RP

based on the histological findings. This may be because wrong position of the biopsy site and/or missing the best timing of the biopsy such as biopsy after initiation of corticosteroid administration (11).

The severity and prognosis of RP largely depends on laryngo-tracheal and/or cardiovascular involvement. It has been reported that laryngo-tracheal manifestations were seen in approximately 20%- 50% (10, 13) of all RP patients and one fourth of patients with airway involvement were treated with tracheotomy (13). It is reported that the main cause of death is airway collapse and/or pulmonary infection, while airway symptoms were first manifestation in only 20% of RP patients with laryngo-tracheal involvement (14). These airway profiles were almost similar in this Japanese retrospective study.

In this survey, CT scan was conducted 38% of the patients in Japan. We rather recommend routine CT examination of the chest to find out lower respiratory tract involvement by expiratory phase scanning (13, 15, 16), and hopefully subclinical stenosis of bronchus. Several researchers also pointed out that tracheal wall thickness in CT scan was very important to the diagnosis of RP (15-18). Miyazawa T et al. described the endobronchial ultrasonography was useful in the diagnosis and treatment of RP (19).

There are a lot of case reports observing the efficacy of prednisolone and immunosuppressant to the airway symptoms (20). Recent studies reported the possibility that corticosteroid and immunosuppressant

combination therapy may avoid the progression of airway involvement (21, 22).

In agreement with the above reports (20–22), our study revealed that all patients with airway involvement who had been treated with corticosteroid monotherapy resulted in tracheotomy, suggesting the insufficiency of corticosteroid monotherapy for the prevention of airway disease progression (Fig. 2). Therefore, we strongly recommend combination therapy of corticosteroid and immunosuppressant for those with airway involvement, even though the involvement is in their early phases.

Several studies reported the usefulness of interventions, such as balloon dilatation and stenting therapy. Our study and our own clinical experiences totally support this notion. Sarodia et al. mentioned successful uses of self-expanded metallic tracheobronchial stents (23). Ernst A et al. reported the usefulness of the silicone stent (13). They also described the progression of airway involvement even under their intervention and we recommend sufficient corticosteroid and immunosuppressant be administered to those patients.

It has been reported that cardiac involvement were seen in 15-46% of RP patients (10, 24) and second cause of RP death. It was more prominent in the male populations, while the ratio of female/male was even in whole RP patients. This complication includes aortic regurgitation and mitral regurgitation, myocarditis, pericarditis, heart block, ischemia, paroxysmal atrial tachycardia, and large artery aneurysm. In this study, we found that

cardiovascular involvement was less frequent in Japan (7.1 %) as compared with other reports (15-46%). The reason for this discrepancy remains obscure.

Dib C et al. reported the retrospective chart review of 33 patients with cardiac surgery (25). We agree their recommendation that ultrafast chest computed tomography, magnetic resonance imaging, or transesophageal echocardiography are important because cardiac involvement can be totally asymptomatic.

There were a few accounts of the study about the biological therapy on RP. First of all, Leroux et al. reported that Rituximab was not effective to RP in his retrospective study (26). We found several case reports showing the effectiveness of anti-cytokine agents, such as infliximab (27), adalimumab (28) and anakinra (29, 30). Based on this survey, we can not get any conclusion of the effectiveness of these biologics on RP at present. Some patients were obviously refractory to the biologics. Kraus et al. reported that MCP-1, MIP-1beta, and IL-8 were significantly higher in RP patients (31). We need to elucidate cytokine involvement in the pathophysiology of RP.

In conclusion, we described here the initial Japanese large retrospective study of RP, and also mentioned two major complications of RP to understand the clinical aspect. We found that corticosteroid + immunosuppressant combination therapy was better than corticosteroid monotherapy for controlling airway involvement of RP. Further study is necessary to improve

clinical outcome of this disease.

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Table 1. Summary of questionnaire used in this survey.

1. Patient profile

Age at onset of the disease

Age at diagnosis

Sex

Duration of follow-up

2. Clinical feature

First and/or consequent symptoms as following:

auricular chondritis

vestibular dysfunction

reduced hearing

arthritis

nasal chondritis

saddle nose

eye involvement

laryngotracheal involvement

cardiovascular involvement

skin involvement

nervous system involvement

kidney disease

3. Examminations for diagnosis

Main laboratory features

image analysis

histopathologic features

4. Treatment (safety and efficacy)

NSAID

Steroid

Immunosuppressive

Antibiotics

Surgical intervention

Others

5. Prognosis and complications

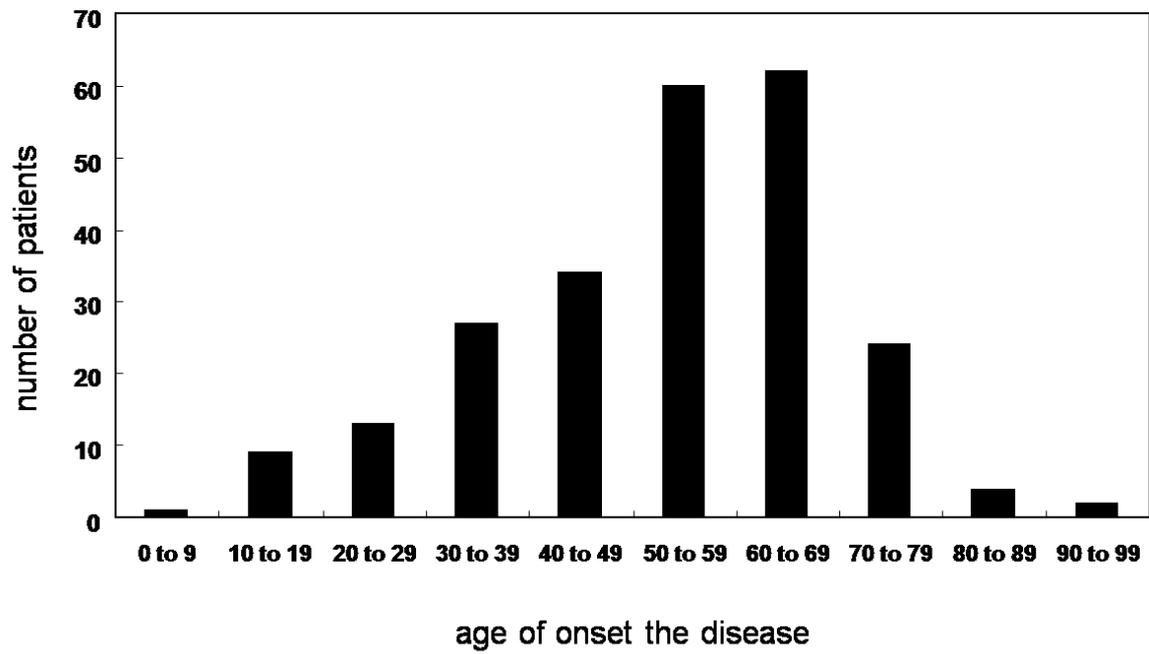
Table 2. Frequency of clinical lesions in 239 Japanese patients with RP

| Clinical lesions | frequency | (number of patients) |
|------------------|-----------|----------------------|
| External ear | 78.2 % | (187) |
| Internal ear | 26.8 % | (64) |
| Nasal cartilage | 39.3 % | (94) |
| Airway | 49.8 % | (119) |
| Laryngo | 17.2 % | (41) |
| tracheobronchial | 33.9 % | (81) |
| Eye | 45.6 % | (109) |
| conjunctiva | 14.6 % | (35) |
| sclera | 26.4 % | (63) |
| uveal | 10.5 % | (25) |
| Arthro | 38.5 % | (92) |
| Skin | 11.4 % | (32) |
| Cardiovascular | 7.1 % | (17) |
| Neurological | 9.6 % | (23) |
| Renal | 6.7 % | (16) |
| Bone marrow | 2.1% | (5) |

Table 3. Effective rate of immunosuppressants

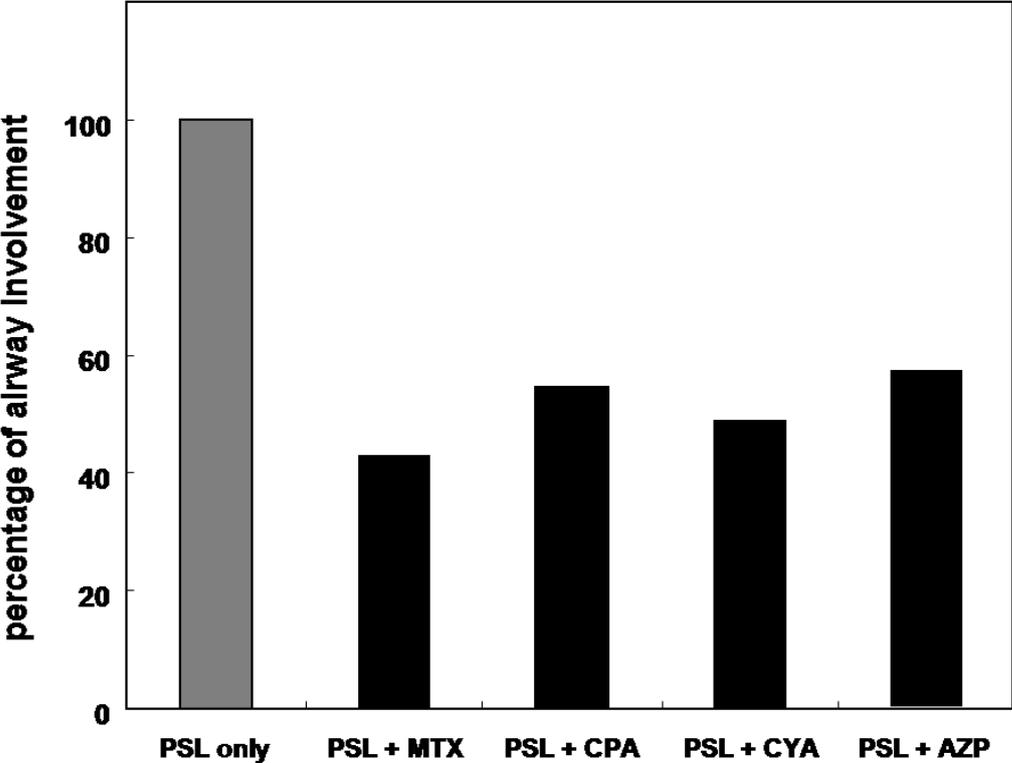
| Therapy | Effective | non-effective | unknown |
|---------|-----------|---------------|---------|
| MTX | 64.0 % | 16.0 % | 20.0 % |
| CPA | 66.7 % | 20.0 % | 14.3 % |
| CYA | 73.7 % | 26.3 % | 0.0 % |
| AZP | 37.5 % | 41.7 % | 20.8 % |

Figure 1. The distribution of age at the disease onset of RP.



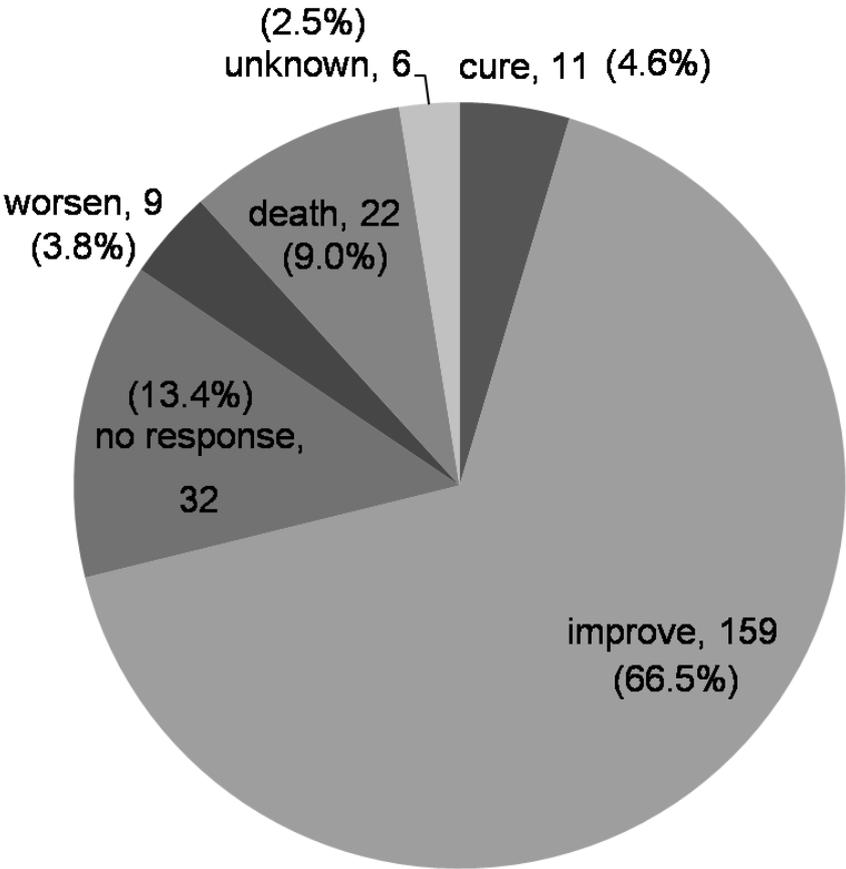
Total number of the patients was 239. The mean age at onset of disease was 52.7 years old, with a range from 3 to 97 years old.

Figure 2. The percentage of airway involvement for the sort of immunosuppressant.



Higher rate of airway involvement was seen in the patients treated with PSL only. Abbreviation PSL: prednisolone MTX: methotrexate, CPA: cyclophosphamide, CYA: cyclosporine.

Figure 3. The overall prognosis of Japanese patients with RP.



72 % of our cohort responded to the treatment in some extent. 17.2% of patients showed no response, and 9.0 % of patients were dead.

本邦における再発性多発軟骨炎の疫学調査研究 (第一報：臨床像および治療の実態調査 102 例の報告)

第 20 回日本リウマチ学会関東支部学術集会

会期：平成 21 年 12 月 6 日（日）

場所：神奈川県横浜市（パシフィコ横浜会議センター）

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目的： 再発性多発軟骨炎 (relapsing polychondritis: RP) は、原因不明の稀な難治性疾患であるが、本邦における疫学調査や病態解明の研究は未だ不十分である。我々は、本邦における RP の臨床像および治療の実態を明らかにするため疫学調査を実施した。

方法： 全国基幹医療機関・施設の RP 診療担当科（耳鼻咽喉科、呼吸器科、リウマチ科等）の医師を対象に疫学調査（記入アンケート方式）を行い、RP 臨床像と治療の実態を解析した。

結果： 一次調査票 1050 通の送付に対して 470 通の回答があり、そのうち RP 症例「治療経験有り」の回答は 206 通、「経験なし」の回答は 264 通であった。次に二次調査票 369 通を送付し、70 施設から回答があり 102 症例の臨床情報を得た。RP 102 例の解析では、平均発症年齢 53.4 歳 (3~82 歳: 男性 55 例、女性 46 例)、初発症状として 55 例 (53.4%) に耳介軟骨炎がみられた。気道病変 (気管軟骨炎、喉頭軟骨炎) 56 例 (54.4%)、骨髄異形成症候群 4 例 (4.3%)、白血病 1 例も観察された。102 例中 94 例 (92.2%) にステロイド治療歴があり、免疫抑制剤治療ならびに生物学的製剤は気管軟骨炎を伴う重症例で用いられる傾向にあった。気道病変に対しては 24 例 (23.5%) に気管切開、11 例 (10.8%) に気管内ステント挿入、8 例 (7.8%) に二相式気道陽圧療法が施行されていた。RP 102 例の臨床経過は、治癒・改善が 71%、不変 10%、悪化 2%、死亡が 15%であった。

結語： 本邦 RP 102 例の疫学調査結果から臨床像および治療の実態を詳解し報告する。

本邦における再発性多発軟骨炎の疫学調査研究 (臨床像および治療の実態調査162例の報告)

第54回日本リウマチ学会総会・学術集会

会期：平成22年4月22日(木)～25日(日)

場所：兵庫県神戸市(神戸ポートピアホテル)

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目的： 再発性多発軟骨炎(relapsing polychondritis: RP)の臨床像および治療の実態を明らかにするため疫学調査を実施した。

方法： RPの症例報告のある医療機関および全国基幹医療機関・施設のRP診療担当科の医師を対象に疫学調査(記入アンケート方式)を行い、RP臨床象と治療の実態を解析した。

結果： 120施設から回答があり162症例の臨床情報を得た。RPの162例の解析では、平均発症年齢53.6歳(3～82歳：男性85例、女性77例)、初発症状として90例(55.5%)に耳介軟骨炎がみられた。気道病変(気管軟骨炎、喉頭軟骨炎)97例(59.9%)が観察された。162例中149例(91.9%)にステロイド治療歴があり、免疫抑制剤治療ならびに生物学的製剤は気管軟骨炎を伴う重症例で用いられていた。RP162例の臨床経過は、治癒・改善が70%、不変13%、悪化4%、死亡が11%であった。