G. 研究発表

1. 論文発表

1. Oka H, Yamano Y, Shimizu J, Yudo K, Suka M, Suzuki N. Nationwide epidemiologic study of relapsing polychondritis in Japan; results of 239 cases. (submitted for publication).

2. 学会発表

1. 岡寛、遊道和雄、山野嘉久、鈴木登、尾崎承一、須賀万智. 本邦における再発性多発軟骨炎の疫学調査研究 102 例の報告、 第 20 回日本リウマチ学会関東支部学術集会、2009 年 12 月.

2. 鈴木登、山野嘉久、岡 寛、遊道和雄. -再発性多発性軟骨炎-治療研究中間報告会、2009 年 9 月 27 日

H. 知的財産権の出願・登録状況

1. 特許取得：

本研究で同定した新規分子に関して、RP 患者における診断マーカー・疾患活動性マーカー・治療標的として特許申請準備中である。

2. 実用新案登録：なし

図 1 RP 患者における血清中の各種サイトカイン・ケモカインの定量的解析

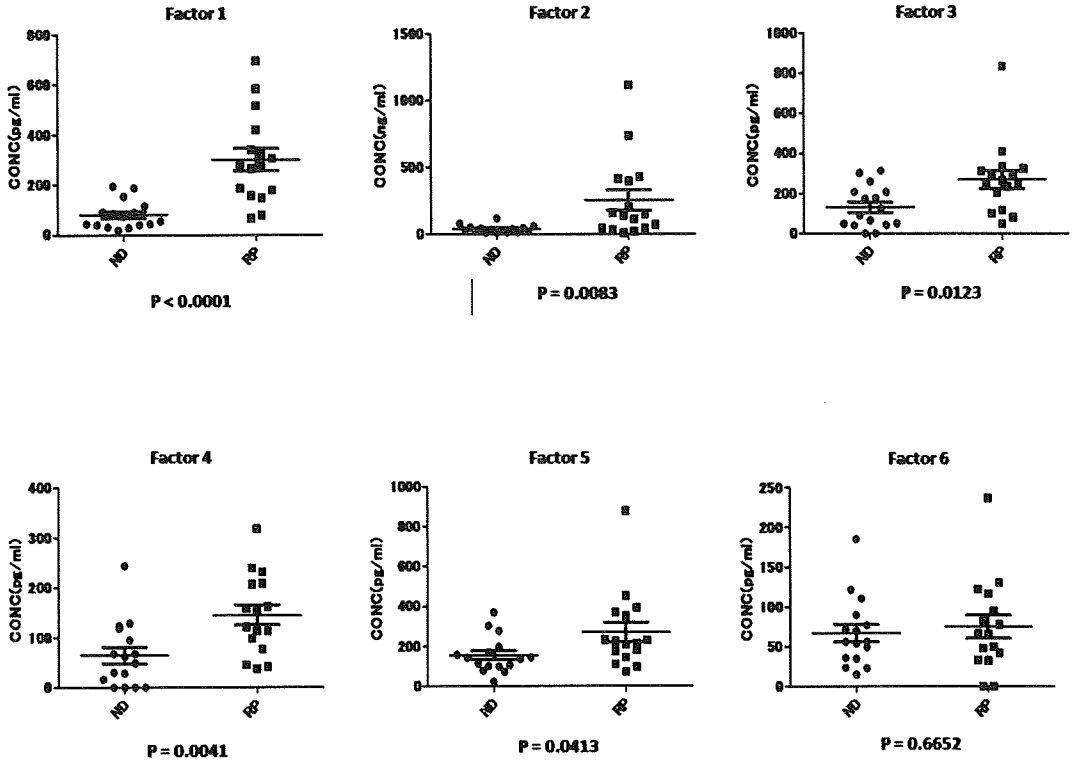
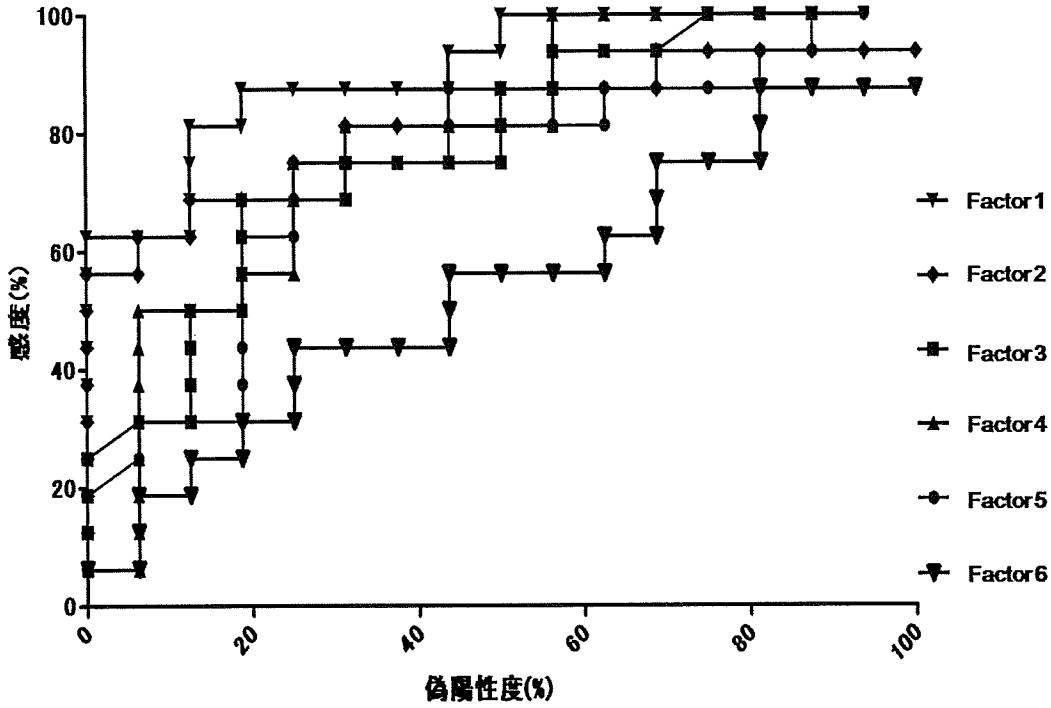


図２ RP 患者血清中バイオマーカー候補因子の ROC 曲線による解析



Ⅲ．研究成果の発表に関する一覧表

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投稿中

1．Oka Hiroshi, Yudo Kazuo, Yamano Yoshihisa, Shimizu Jun, Suzuki Noboru: Nationwide Epidemiologic Study of Relapsing Polychondritis in Japan; results of 239 cases. Annals of Rheumatic Disease.

学会発表

1．Teruomi Miyazawa, et al.Migration of choke point in relapsing polychondiritis after stening. The American College of Chest Physicians 2009, San Diego, Oct. 31-Nov. 5, 2009.

2．岡　寛、遊道和雄、山野嘉久、清水　潤、須賀万智、尾崎承一、鈴木 登：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：平成21年12月6日、横浜

3．岡　寛、遊道和雄、山野嘉久、清水　潤、須賀万智、尾崎承一、鈴木 登：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：平成22年4月22日ー25日、神戸

Ⅳ. 研究成果の刊行物・別刷

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

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Running title: Epidemiology of Relapsing Polychondritis in Japan

This work was supported in part by a Grant-in The Japanese Ministry of Health, Labour, and Welfare.

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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 questionnnaire 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. Endobrochial 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-cartilagious 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)-a and interleukin (IL)-6 in autoimmune diseases such as rheumatoid arthritis, and the subsequent introduction of the anti-TNF-aagents 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 forth 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 tracheobroncheal 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 pathophisiology 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.

Acknowledgments

We thank M. Kondo for her excellent technical assistance.

References

1. Trentham DE, Le CH. Relapsing polychondritis. Ann Intern Med 1998;129:114-122.
2. Letko E, Zafirakis P, Baltatzis S, Voudouri A, Livir-Rallatos C, Foster CS. Relapsing polychondritis: a clinical review. Semin Arthritis Rheum 2002;31:384-395.
3. Kent PD, Michet CJ, Luthra HS. Relapsing polychondritis. Curr Opin Rheumatol 2004;16:56-61.
4. Gergely P Jr, Poór G. Relapsing polychondritis. Best Pract Res Clin Rheumatol 2004;18:723-738.
5. Luthra HS. Relapsing polychondritis. In Klippel JH, Dieppe PA, eds. Rheumatology vol27 St. Louis, Mosby 1998:1-4.
6. Ananthakrishna R, Goel R, Padhan P, Mathew J, Danda D. Relapsing polychondritis--case series from South India. Clin Rheumatol 2009;28:S7-10.
7. Sharma A, Bambery P, Wanchu A, Sharma YP, Panda NK, Gupta A, et al. Relapsing polychondritis in North India: a report of 10 patients. Scand J Rheumatol 2007;36:462-465.
8. Kong KO, Vasoo S, Tay NS, Chng HH. Relapsing polychondritis--an Oriental case series. Singapore Med J 2003;44:197-200.
9. Damiani JM. Levine HL. Relapsing polychondritis. Report of ten cases. Laruygoscope (St.Lous). 1979;89:929-946.
10. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM. Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore) 1976;55:193-215.
11. Chauhan S, Agarwal V, D'Cruz S. Case 14-2007: a man with pain and swelling of both eyes and the right ear. N Engl J Med 2007;356:1980-1988.
12. Valenzuela R, Cooperrider PA, Gogate P, Deodhar SD, Bergfeld WF. Relapsing polychondritis. Immunomicroscopic findings in cartilage of ear biopsy specimens. Hum Pathol 1980;11:19-22.
13. Ernst A, Rafeq S, Boiselle P, Sung A, Reddy C, Michaud G, et al. Relapsing polychondritis and airway involvement. Chest 2009;135:1024-30.
14. Michet CJ Jr, McKenna CH, Luthra HS, O'Fallon WM. Relapsing polychondritis. Survival and predictive role of early disease manifestations. Ann Int Med 1986;104:74-78.
15. Behar JV, Choi YW, Hartman TA, Allen NB, McAdams HP. Relapsing polychondritis affecting the lower respiratory tract. AJR 2002;178:173-177.
16. Tillie-Leblond I, Wallaert B, Leblond D, Salez F, Perez T, Remy-Jardin M, et al. Respiratory involvement in relapsing polychondritis. Clinical, functional, endoscopic, and radiographic evaluations. Medicine (Baltimore) 1998;77:168-176.
17. Im JG, Chung JW, Han SK, Han MC, Kim CW. CT manifestations of tracheobronchial involvement in relapsing polychondritis. J Compute Assist Tomogr 1988;12:792-793.
18. Faix LE, Branstetter BF 4th. Uncommon CT findings in relapsing polychondritis. Am J Neuroradiol 2005;26:2134-2136.
19. Miyazu Y, Miyazawa T, Kurimoto N, Iwamoto Y, Ishida A, Kanoh K, et al. Endobronchial ultrasonography in the

diagnosis and treatment of relapsing polychondritis with tracheobronchial malacia. Chest 2003;124:2393-2395.
20. Lipnick RN, Fink CW. Acute airway obstruction in relapsing polychondritis: treatment with pulse methylprednisolone. J Rheum 1991;18:98-99.
21. Yamaoka K, Saito K, Hanami K, Nakayamada S, Nawata M, Iwata S, et al. A case of life-threatening refractory polychondritis successfully treated with combined intensive immunosuppressive therapy with methotrexate. Mod Rheum 2007;17:144-147.
22. Belot A, Duquesne A, Job-Deslandre C, Costedoat-Chalumeau N, Boudjemaa S, Wechsler B, et al. Pediatric-Onset Relapsing Polychondritis: Case Series and Systematic Review. J Pediatr 2009 [Epub ahead of print]
23. Sarodia BD, Dasgupta A, Mehta AC. Management of airway manifestations of relapsing polychondritis: case reports and review of literature. Chest 1999;116:1669-1675.
24. Michet CJ. Vasculitis and relapsing polychondritis. Rheum Dis Clin North Am 1990;16:441-444.
25. Dib C, Moustafa SE, Mookadam M, Zehr KJ, Michet CJ Jr, Mookadam F. Surgical treatment of the cardiac manifestations of relapsing polychondritis: overview of 33 patients identified through literature review and the Mayo Clinic records. Mayo Clin Proc 2006;81:772-776.
26. Leroux G, Costedoat-Chalumeau N, Brihaye B, Cohen-Bittan J, Amoura Z, Haroche J, et al. Treatment of relapsing polychondritis with rituximab: a retrospective study of nine patients. Arthritis Rheum 2009;61:577-582.
27. Ghosn S, Malek J, Shbaklo Z, Matta M, Uthman I. Takayasu disease presenting as malignant pyoderma gangrenosum in a child with relapsing polychondritis. J Am Acad Dermatol 2008;59:S84-87.
28. Seymour MW, Home DM, Williams RO, Allard SA. Prolonged response to anti-tumour necrosis factor treatment with adalimumab (Humira) in relapsing polychondritis complicated by aortitis. Rheumatology 2007;46:1739-1741.
29. Wendling D, Govindaraju S, Prati C, Toussirot E, Bertolini E. Efficacy of anakinra in a patient with refractory relapsing polychondritis. Joint Bone Spine 2008;75:619-625.
30. Vounotrypidis P, Sakellariou GT, Zisopoulos D, Berberidis C. Refractory relapsing polychondritis: rapid and sustained response in the treatment with an IL-1 receptor antagonist (anakinra). Rheumatology 2006;45:491–492.
31. Stabler T, Piette JC, Chevalier X, Marini-Portugal A, Kraus VB. Serum cytokine profiles in relapsing polychondritis suggest monocyte/macrophage activation. Arthritis Rheum 2004;50:3663-3667.

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 efficasy)
    - NSAID
    - Steroid
    - Immunosuppresive
    - 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)

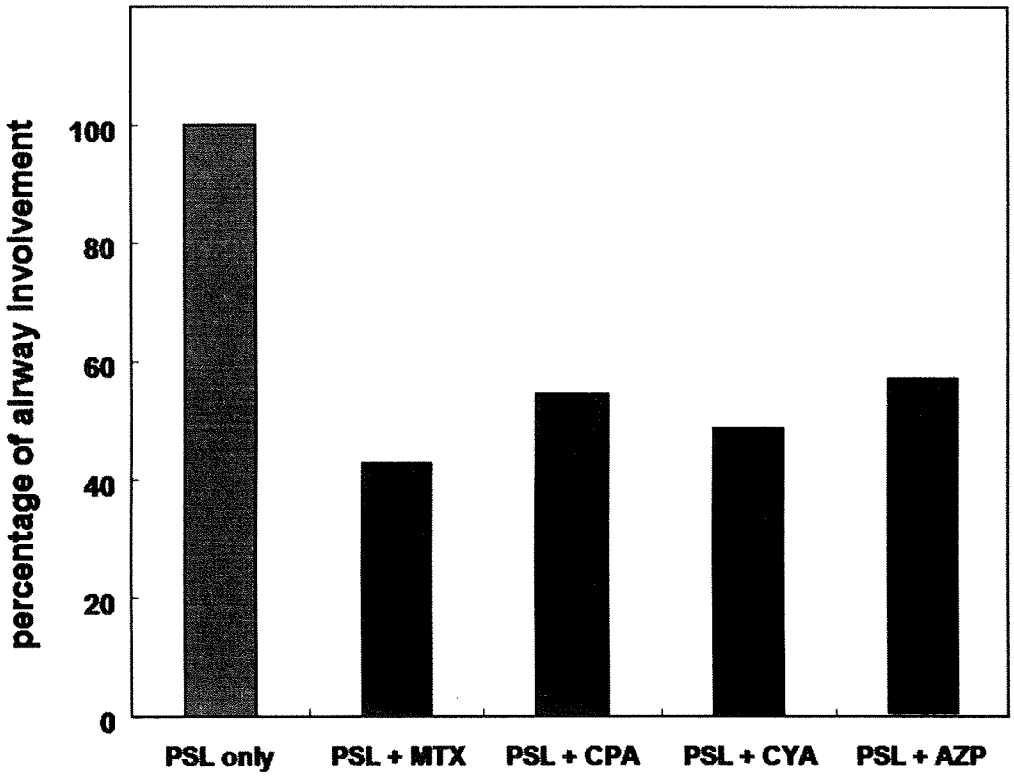
Table 3. Effective rate of immunosuppressants

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.

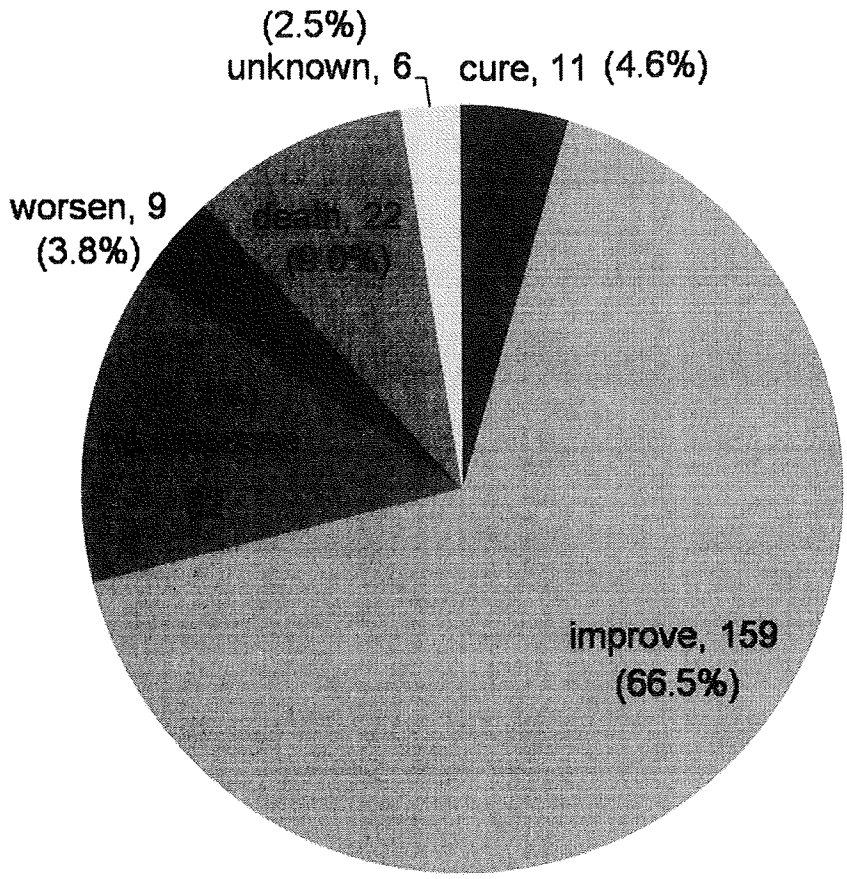
Total number of the patients was 239. The mean age at onset of disease was 52.7 years old, with a range from 3 to 97 years old.

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.