dose of prednisolone for maintenance. Minocycline hydrochloride was used in 8 patients with RP but obvious effects were not noted

Immunosuppressants 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 air involvements. CPA or AZP treatment in conjunction with steroid administration also showed a significant decrease of airway involvement (54.5% and 57.0%, respectively) while controlling symptoms (Figure 2).

Since 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 RP.

In our survey, infliximab treatment resulted in a response in 6 cases of 10 RP patients with airway involvement that had not responded to conventional immunosuppressants (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 which were reported in this survey were not sufficient to assess the efficacy and toxicity of these therapeutic agents in RP.

Prognosis

We also summarized the overall prognosis of our cohort (Figure 3). 11 patients (4.6%) were 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), MDS (1 patient), leukemia (1 patient), unknowun (2 patients).

DISCUSSION

RP is characterized by recurrent and potentially severe inflammation of cartilaginous structure of the external ear, nose, peripheral joints and laryngo-tracheal organ. Cardiovascular tissue and eye were also involved because of its proteoglycan-rich structure.

We send our questionnaire to totally 395 experienced MD who belonged to university hospitals and national, public and larger private hospitals. Their specialties include departments of immunology, rheumatology, radiology, otopharyngolaryngology, internal medicine, dermatology, respiratory medicine and so on.

The diagnosis of RP was made depending upon the clinical features and pathological finings of chondritis, because no specific laboratory tests exist (9). 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 (10). Indeed, in this study histological examination of biopsied specimen was conducted in 228 cases out of 239 cases (95.4%). Typical pathological findings were present in 138 cases out of 228 cases who had histological examination. However, 90 cases were difficult to make a firm diagnosis of RP with 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 steroid administration.

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% (11, 12) of all RP patients and one forth of patients with airway involvement were treated with tracheotomy (11). It is reported that the main cause of death is air way collapse and/or pulmonary infection, while air way symptoms were first manifestation in only 20% of RP patients with laryngo-tracheal involvement (13). These airway profiles were almost similar to the tendencies 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, and hopefully subclinical stemosis of bronchus. Behar JV et al. pointed out tracheal wall thickness in CT scan was very important to the diagnosis of RP (14-16). Dynamic expiratory CT scan is useful to evaluate patients air way but the range of sensitivity was wide (11, 17). Miyazawa T et al. described the endobronchial ultrasonography was useful in the diagnosis and treatment of RP (18).

There are a lot of case reports observing the efficacy of prednisone and immunosuppressant to the air way symptom (19). Recent studies reported the possibility that corticosteroid therapy and immunosuppressant combination may avoid the progression of air way involvement (20, 21).

In agreement with the above reports (19—21), 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 (Table 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 (22). Ernst A et al. reported the usefulness of the silicone stent.(11) They also described the progression of air way involvement even under their intervention and we recommend sufficient corticosteroid and immunosuppresant be administered to those patients.

It has been reported that cardiac involvement were seen in 15-46% RP patients (12, 23) and second cause of RP death. It was more prominent in the male populations, while the ratios of female/male were even or high in whole RP patients. This complication includes aortic regurgitation and mitral regurgitation, myocarditis, pericarditis, heart block, ischemia, paroxysmal atrial tachycardia, and large artery aneurusm. 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. Further studies are necessary to confirm this tendency.

Dib C et al. reported the retrospective chart review of 33 patients with cardiac surgery (24). We agree their recommendation that because cardiac involvement can be *totally asymptomatic,* ultrafast chest computed tomography, magnetic resonance imaging, or transesophageal echocardiography important.

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 (25). We found several case reports showed the effectiveness of anti-cytokine antibodies, such as infliximab (26), adalimumab (27) and anakinra (28, 29). 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 (AR2004; 50:3663-3667). Further efforts are need to elucidate cytokine involvement in the pathogenesis 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 + immunosuppresant combination therapy is 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 efficasy)
    - NSAID
    - Steroid
    - Immunosuppresive
    - Antibiotics
    - Surgical intervention
    - Others
5. Prognosis and complications

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

Clinical manifestations	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)
conjunctivitis	14.6 %	(35)
scleritis	26.4 %	(63)
uveitis	10.5 %	(25)
Arthritis	38.5 %	(92)
Skin	11.4 %	(32)
Cardiovascular	7.1 %	(17)
Neurological	9.6 %	(23)
Renal	6.7 %	(16)
MDS	2.1%	(5)

Figure 1

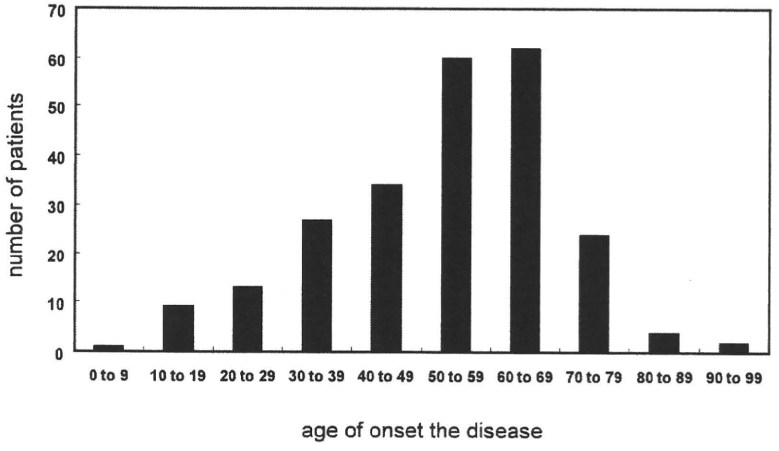


Figure 2

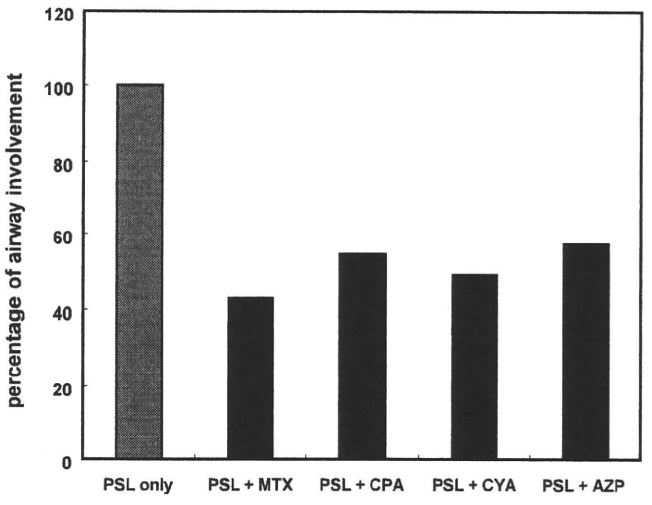
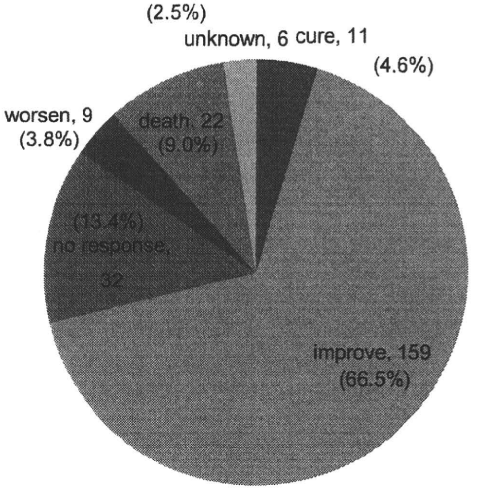


Figure 3



Increased expression of triggering receptor expressed on myeloid cells 1 in patients with relapsing polychondritis

第 55 回日本リウマチ学会総会・学術集会
会期：平成 23 年 4 月 24 日ー27 日
場所：東京都港区（グランドプリンスホテル新高輪　国際館パミール）

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Relapsing polychondritis (RP) is a rare inflammatory disorder of unknown aetiology. Most RP patients show elevated CRP levels; however, some RP patients with insidiously advancing fibrosis do not. Therefore, the identification of a more sensitive biomarker is essential for monitoring disease activity. Here, we measured multiple cytokines and chemokines quantitatively in the serum samples of 16 RP patients and 16 HDs by using enzyme-linked immunosorbent assay or cytometric bead array. The serum levels of sTREM-1, IFN-γ, MIP-1β, MMP-3, VEGF, and IP-10 in RP patients were significantly higher than those in HDs. Among these molecules, sTREM-1 had the highest sensitivity. Thus, our findings showed that compared to other molecules such as CRP, sTREM-1 might be a better biomarker of RP. (790 letters)

再発性多発軟骨炎患者における血清中の可溶性 TREM-1 濃度の上昇

再発性多発軟骨炎（Relapsing polychondritis：RP）は、全身軟骨の慢性炎症を特徴とし、原因不明で稀な難治性疾患である。その疾患活動性の評価は、一般的に血清中 CRP が用いられているが、CRP が正常範囲内であっても気道軟骨病変が進行する症例がしばしば認められ、より感度の高い疾患活動性マーカーの同定が求められる。そこで我々は、RP 患者 16 例と健常者 16 例の血清を用いて、様々なサイトカインやケモカインなどの ELISA 法や cytometric bead array 法を用いた定量的解析を行い、RP 患者において sTREM-1, IFN-γ, MIP-1β, MMP-3, VEGF, IP-10 が有意に上昇している事、さらにこれらの中で、sTREM-1 が最も感度に優れている事を明らかにし、RP 患者における疾患活動性マーカーとして、血清中 sTREM-1 が有用である可能性が示唆された。（399 文字）

再発性多発軟骨炎31例の患者の実態調査

第55回日本リウマチ学会総会・学術集会
会期：平成23年4月24日ー27日
場所：東京都港区（グランドプリンスホテル新高輪　国際館パミール）

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（目的）再発性多発軟骨炎（RP）患者にアンケート方式の医療実態調査を行う。
（方法）RP患者支援会の協力を得て、全国のRP 31例の受診科、月額医療費、公的補助の有無を調査した。
（結果）31人（男性7人,女性24人）の平均年齢は45.9歳であった。平均診療科数は、2.74科であり、リウマチ免疫科が最多であった。平均月額医療費は、外来患者が16,774円であり、入院患者では、200,702円であった。公的補助は31例中4例(12.9%)のみであった。
（結語）本邦のRP患者は、複数科を受診し、多額の医療費を強いられていた。特に気道の合併症のため、入院した場合は、月額医療費は20万円を超える高額になっていた。

Ⅴ．平成22年度班員名簿

平成 22 年度　難治性疾患克服研究事業

研究分野	ライフサイエンス		
研究課題名	難治性疾患克服研究事業　再発性多発軟骨炎の診断と治療体系の確立		
課題番号	H22－難治－一般－088		
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