Title page

Field: Inflammation

Types of manuscript: Full papers

Title: A large-scale survey of patients with relapsing polychondritis in Japan

by

Hiroshi Oka, Yoshihisa Yamano, Jun Shimizu, Kazuo Yudoh, Noboru Suzuki.

Institute of Medical Science and Departments of Immunology and Medicine

St. Marianna University School of Medicine

Kawasaki 216-8512, Japan

Address correspondence; Noboru Suzuki, MD, PhD, Institute of Medical Science, St. Marianna University School of Medicine, 2-16-1, Sugao, Miyamae-ku, Kawasaki 216-8512 Japan

Tel; 81-44-977-8111 (ext, 3547)

Fax; 81-44-975-3315

E-mail; n3suzuki@marianna-u.ac.jp

Short running title: Airway involvement in relapsing polychondritis (42)

Abstract (247 words)

Relapsing polychondritis (RP) is a multisystem disorder characterized by recurrent inflammation and destruction of cartilage. The aim of this study is to assess the clinical characteristics of patients with RP in Japan, which remain unclear.

A survey was sent to 395 experienced clinicians who worked in Japanese major institutions. The questionnaire was designed to assess patients' profiles, clinical features, diagnosis, treatments and present complications. The response rate was 30.6% and 239 RP patient data were collected.

The average age of onset diagnosis was 52.7 years (range, 3-97) and the male-to-female ratio was 1.1:1. Clinical features of patients with RP in Japan were similar to previous studies. Airway and cardiac involvement, both of which were potentially serious complications of RP, were observed in 119 (49.8%) and 17 patients (7.1 %), respectively. Four patients (1.7%) had myelodysplasia. In addition to oral prednisolone (91.6%), patients received methotrexate (19.7%), cyclophosphamide (12.6%) and cyclosporine (8.4%) with clinical response rates of 64.0%, 66.7% and 73.7%, respectively.

42 patients (17.6%) required and underwent tracheotomy, including 12 patients (5.0%) who were treated with prednisolone only. 22 patients (9.2%) underwent stent placement and/or tracheotomy. The overall mortality rate was 9.0% (22 patients) and respiratory failure and pulmonary infection were the leading causes of death in patients with RP.

Airway involvement of RP was fundamentally progressive and required frequent clinical checks and appropriate intervention with administration of both prednisolone and immunosuppressant. Cardiac involvement of RP was less common in

63

Japan as compared with that in Western countries.

Introduction

Relapsing polychondritis (RP) is an uncommon inflammatory disorder of unknown etiology that affects the cartilage of ear, nose, peripheral joints, and respiratory tract[1-4]. Other proteoglycan-rich tissues such as eye, inner ear, heart, blood vessels, and kidneys are also involved[1-4]. When the visceral is affected by inflammation, RP is a potentially lethal disease.

The epidemiological studies of this disease have been conducted 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 case series with a decade of RP patient data have been reported from South/North India[6, 7] and Singapore[8].

In 2012, RP Disease Activity Index (RPDAI), a preliminary score for assessing disease activity, was developed by worldwide specialists[9]. Nonetheless, even now, physicians treat patients with RP on the basis of largely empirical evidence because of the lack of large-scale survey and clinical guidelines for the management of patients.

Here, we conducted a survey of 239 patients with RP to outline the current epidemiology, clinical manifestations, management and long-term outcome of RP in Japan.

Subjects and Methods

A Multi-institutional study survey of Japanese major medical facilities was conducted from July to December 2009. All subjects who were sent the questionnaire were informed of the purpose of the study and the responses would be kept confidential. All the authors reviewed the questionnaire.

We performed preliminary survey of clinical experience to treat patients with RP in 1894 Japanese medical facilities on July 1st, 2009, using a surveillance definition as follows: larger bed sizes (+200 or university hospitals) and adequate functions for RP treatments (providing services with eye-throat-nose, respiratory, chest surgery, dermatology, neurology and rheumatology divisions). We also reviewed recent Japanese clinical reports and research articles of RP using web accessible medical literature databases made by US National Library of Medicine, Japan Medical Abstracts Society and Japan University hospital Medical Information Network, and sent the initial survey questionnaire to the authors. Then, a main survey was sent to the 395 physicians who have returned a mail to us that the physicians have been treating or treated at least one patient with RP on August 14th, 2009. The patient data of the survey questionnaire were collected anonymously. This survey was approved by the ethics committee of St. Marianna University School of Medicine.

The questionnaire consisted of 5 sections to assess patients' (a) profiles, (b) clinical features, (c) diagnosis, (d) treatments and (e) present complications. It was summarized in Table 1. We asked the physicians to give us the most current laboratory findings with respiratory function except the titers of anti-type II collagen antibody and pathological findings.

Results

The survey response rate was 30.6% (121 of 395 surveyed physicians) and 239 RP patient data were collected.

Patients' profiles

Patient characteristics in McAdam series[10] and current survey were summarized in Table 2. The male-to-female ratio was 1.13:1 (127 males and 112 females). Uni-modal

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 artery[2] 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 patients[11]. 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 States[5].

The disease severity and prognosis of RP largely depends on airway and cardiovascular involvement[10]. 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 infection[12-14]. 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 scan[12]. Miyazawa et al. described the

endobronchial ultrasonography was useful to indicate fragmentation and edema of cartilage in patients with RP[11].

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 complications[20]. 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 patients[20].

Certainly, several reports have described the latent phase of cardiovascular complications for a few years after the onset of RP in relatively young patients[21-24]. 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 well[33]. 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 finings of chondritis[28]. 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 tissue[34].

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 inflammation[28].

In laboratory experiments of biopsy specimen, immunoglobulin and C3 component of complement deposited to margin of cartilage and perichondrial vessel wall[34]. Antibody to type II collagen was detected in patients with RP from the disease onset and the titers were correlated with disease activity[35]. Hyper-activation of macrophage/monocytes in peripheral blood of RP patients was reported using cytokine profile analysis[36].

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 activity[37]. 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 infliximab[42], adalimumab[43], anakinra[44, 45] and abatacept[46]. 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.

Disclosure

All authors have no conflict of interest.

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; Rheumatology. (eds. Klippel JH, Dieppe PA), Mosby Inc, St. Louis; 1998. Vol. 27, pp1-4.

6) Ananthakrishna R, Goel R, Padhan P, Mathew J, Danda D: Relapsing polychondritis-case series from South India. Clin Rheumatol. 2009; 28 Suppl 1: S7-10.

7) Sharma A, Bambery P, Wanchu A, Sharma YP, Panda NK, Gupta A, Singh S: 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) Arnaud L, Devilliers H, Peng SL, Mathian A, Costedoat-Chalumeau N, Buckner J, Dagna L, Michet C, Sharma A, Cervera R, Haroche J, Papo T, D'Cruz D, Arlet P, Zwerina J, Belot A, Suzuki N, Harle JR, Moots R, Jayne D, Hachulla E, Marie I, Tanaka T, Lebovics R, Scott D, Kucharz EJ, Birchall M, Kong KO, Gorochov G, Amoura Z; RPDAI study group: The Relapsing Polychondritis Disease Activity

Index: development of a disease activity score for relapsing polychondritis. Autoimmun Rev. 2012; 12: 204-209.

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) Miyazu Y, Miyazawa T, Kurimoto N, Iwamoto Y, Ishida A, Kanoh K, Kohno N: Endobronchial ultrasonography in the diagnosis and treatment of relapsing polychondritis with tracheobronchial malacia. Chest. 2003; 124: 2393-2395.

12) Ernst A, Rafeq S, Boiselle P, Sung A, Reddy C, Michaud G, Majid A, Herth FJ, Trentham D: Relapsing polychondritis and airway involvement. Chest. 2009; 135: 1024-1030.

13) Eng J, Sabanathan S: Airway complications in relapsing polychondritis. Ann Thorac Surg. 1991; 51: 686-692.

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 Am J Roentgenol. 2002; 178: 173-177.

16) 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.

17) Faix LE, Branstetter BF: 4th: Uncommon CT findings in relapsing polychondritis. AJNR Am J Neuroradiol. 2005; 26: 2134-2136.

18) Tillie-Leblond I, Wallaert B, Leblond D, Salez F, Perez T, Remy-Jardin M, Vanhille P, Brouillard M, Marquette C, Tonnel AB: Respiratory involvement in relapsing polychondritis. Clinical, functional, endoscopic, and radiographic evaluations. Medicine (Baltimore). 1998; 77: 168-176.

19) Dolan DL, Lemmon GB Jr, Teitelbaum SL: Relapsing polychondritis. Analytical literature review and studies on pathogenesis. Am J Med. 1966; 41: 285-299.

20) 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.

21) Belot A, Duquesne A, Job-Deslandre C, Costedoat-Chalumeau N, Boudjemaa S, Wechsler B, Cochat P, Piette JC, Cimaz R: Pediatric-Onset Relapsing Polychondritis: Case Series and Systematic Review. J Pediatr. 2010; 156: 484-489.

22) Hidalgo-Tenorio C, Sabio-Sánchez JM, Linares PJ, Salmerón LM, Ros-Die E, Jiménez-Alonso J: Magic syndrome and true aortic aneurysm. Clin Rheumatol. 2008; 27: 115-117.

23) 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.

24) Stein JD, Lee P, Kuriya B, Tenenbaum J, Daniel LB, Butany J, Provost YL, David TE: Critical coronary artery stenosis and aortitis in a patient with relapsing polychondritis. J Rheumatol. 2008; 35: 1898-1901.

25) Kim MK, Park KS, Min JK, Cho CS, Kim HY: A case of polychondritis in a patient with Behçet's disease. Kor J Int Med. 2005; 20: 339-342.

26) Weber F, Kowald E, Schmuth M, Sepp N: Microscopic polyangiitis in a patient with relapsing polychondritis. Rheumatology (Oxford). 2001; 40: 233-235.

27) Coumbaras M, Boulin A, Piette AM, Graveleau P, Blétry O, Pierot L: Intracranial aneurysm associated with relapsing polychondritis. Neuroradiology. 2001; 43: 565-566.

28) 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.

29) Yamazaki K, Suga T, Hirata K: Large vessel arteritis in relapsing polychondritis. J Laryngo Oto. 2001; 115: 836-838.

30) Walker UA, Weiner SM, Vaith P, Uhl M, Peter HH: Aortitis in relapsing polychondritis. Br J Rheumatol. 1998; 37: 1359-1361.

31) Hoang-Xaun T, Foster CS, Rice BA: Scleritis in relapsing polychondritis. Response to therapy. Ophthalmology. 1990; 97: 892-898.

32) Isaak BL, Liesegang TJ, Michet CJ Jr: Ocular and systemic findings in relapsing polychondritis. Ophthalmology. 1986; 93: 681-689.

33) Shinomiya F, Mima N, Nanba K, Tani K, Nakano S, Egawa H, Sakai T, Miyoshi H, Hamada D: Life expectancies of Japanese patients with rheumatoid arthritis: a review of deaths over a 20-year period. Mod Rheumatol. 2008; 18: 165-169.

34) 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.

35) Foidart JM, Abe S, Martin GR, Zizic TM, Barnett EV, Lawley TJ, Katz SI: Antibodies to type II collagen in relapsing polychondritis. N Engl J Med. 1978; 299: 1203-1207.

36) 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.

37) Sato T, Yamano Y, Tomaru U, Shimizu Y, Ando H, Okazaki T, Nagafuchi H, Shimizu J, Ozaki S, Miyazawa T, Yudoh K, Oka H, Suzuki N: Serum level of soluble triggering receptor expressed on myeloid cells-1 as a biomarker of disease activity in relapsing polychondritis. Mod Rheumatol. 2013 Feb 13. [Epub ahead of print]

38) Lipnick RN, Fink CW: Acute airway obstruction in relapsing polychondritis: treatment with pulse methylprednisolone. J Rheumatol. 1991; 18: 98-99.

39) Cohen PR, Rapini RP: Relapsing polychondritis. Int J Dermatol. 1986; 25: 280-285.

40) Mathew SD, Battafarano DF, Morris MJ: Relapsing polychondritis in the Department of Defense population and review of the literature. Semin Arthritis Rheum. 2012; 42: 70-83.

41) Yamaoka K, Saito K, Hanami K, Nakayamada S, Nawata M, Iwata S, Azuma T, Tanaka Y: A case of life-threatening refractory polychondritis successfully treated with combined intensive immunosuppressive therapy with methotrexate. Mod Rheumatol. 2007; 17: 144-147.

42) 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.

43) 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 (Oxford). 2007; 46: 1739-1741.

44) 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.

45) 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 (Oxford). 2006; 45: 491-492.

46) Peng SL, Rodriguez D: Abatacept in relapsing polychondritis. Ann Rheum Dis. 2013; 72:1427-1429.

47) Sarodia BD, Dasgupta A, Mehta AC: Management of airway manifestations of relapsing polychondritis: case reports and review of literature. Chest. 1999; 116: 1669-1675.

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 series[10] 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 (%)	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

Fig. 2

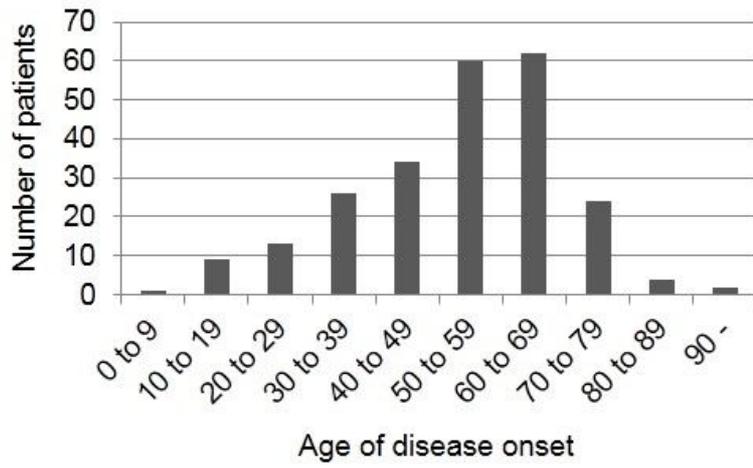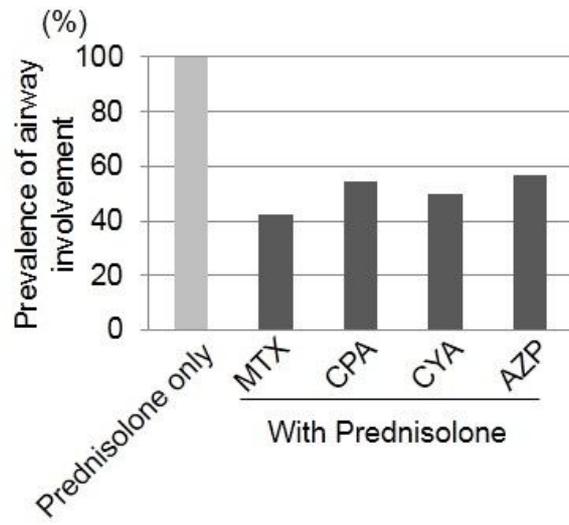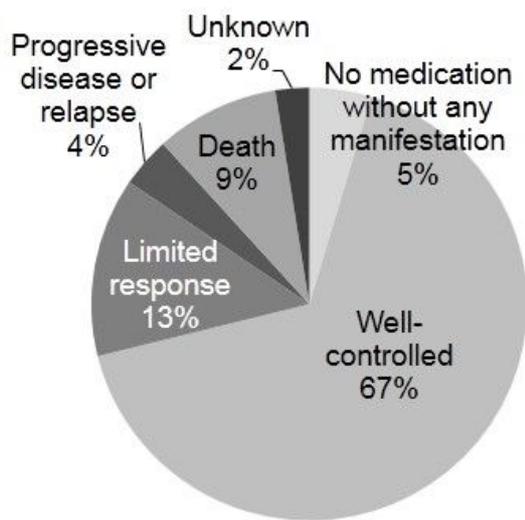Fig. 3