INTRODUCTION

Relapsing polychondritis (RP) is an uncommon autoimmune disease characterized by recurrent inflammation of cartilaginous tissues. It is a multi-organ disease and can be life-threatening and difficult to diagnose. RP mostly occurs between the ages of 40 and 50 years and there is no sex predilection [1]. The cause and pathogenesis remain unclear, but RP is considered an autoimmune disease because it is associated with other autoimmune diseases, responds to corticosteroid therapy [2], and HLA-DR4 antigen and serum anti-type II collagen antibodies are often detected [3].

Most cases are treated with corticosteroid and immunosuppressive agents, but some are not controlled and the inflammation can lead to death.

Larger series of RP patients have been reported, but there are no data on Japanese patients with RP. Here, we present clinical characteristics of 8 Japanese RP patients.
METHODS

The study population was recruited between 2003 and 2017 in Kurume University Hospital. Clinical data, cumulative disease manifestations, laboratory investigations, associated diseases, therapy, clinical courses, disease complications, and outcomes were retrospectively recorded from case notes. The diagnostic criteria for RP proposed by McAdam et al. comprise the following: (1) recurrent chondritis of both auricles, (2) nonerosive inflammatory polyarthritis, (3) chondritis of nasal cartilage, (4) inflammation of ocular structures, including conjunctivitis, keratitis, scleritis, episcleritis, and uveitis, (5) chondritis in the respiratory tract involving laryngeal and/or tracheal cartilages, and (6) cochlear and/or vestibular damage manifesting as sensorineural hearing loss, tinnitus, or vertigo. The diagnosis is certain when 3 or more of these features are present, along with a positive biopsy from the ear, nasal, or respiratory cartilage [2]. Damiani and Levine later suggested that diagnosis could be made when 1 of 3 conditions is met: 3 McAdam criteria, 1 McAdam criterion plus positive histology, or 2 McAdam criteria plus a therapeutic response to steroids or dapsone administration. Biopsy of the involved cartilage is not usually needed if the signs and symptoms are obvious [4].

Ethical approval

The study was conducted in accordance with the Good Clinical Practice guidelines and was approved by the ethics committee of Kurume University (No.

| Table 1. Cumulative characteristics of patients with relapsing polychondritis in previous reports |
|---------------------------------------------------------------|
| **Variables** | McAdam | Michet | Zeuner | Trentham | Kong | Sharma | Ananthakrishna | Dion |
| Number of cases | 1976 | 1986 | 1997 | 1998 | 2003 | 2007 | 2009 | 2016 |
| Demographic characteristics | | | | | | | | |
| Female: male ratio | 76:83 | 55:57 | 13:18 | 49:17 | 3:1 | 6:4 | 5:2 | 86:56 |
| Mean age at diagnosis, year | 44 | 51 | 46.6 | 46 | 34 | 48.1 | 40.2 | 43.5 |
| Mean delay in diagnosis, (range), month | NR | 13-84 | 17-86 | 16-68 | 3-65 | 26-65 | 28-54 | NR |
| Clinical features, % | | | | | | | | |
| Auricular chondritis | 89 | 85 | 94 | 95 | 83 | 100 | 57 | 89 |
| Arthritis | 81 | 52 | 53 | 85 | 75 | 80 | 43 | 69 |
| Laryngotracheal involvement | 56 | 48 | 30 | 67 | 50 | 20 | 43 | 43 |
| Ocular involvement | 65 | 51 | 50 | 57 | 67 | 50 | 43 | 56 |
| Nasal chondritis | 72 | 54 | 56 | 48 | 33 | 50 | 71 | 63 |
| Reduced hearing | 46 | 30 | 19 | 42 | 17 | 40 | 14.3 | 27 |
| Vestibular involvement | NR | 13 | 23 | 53 | 42 | NR | NR | 34 |
| Skin involvement | 17 | 28 | 24 | 83 | 0 | 30 | 14.3 | 28 |
| Saddle nose | NR | 29 | 23 | 20 | 17 | NR | NR | 15 |
| Cardiac involvement | 9 | 6 | 23 | 8 | 8 | 10 | 14.3 | 27 |
| Vasculitis | 18 | 10 | 0 | 12 | 0 | NR | NR | NR |
| Nervous system involvement | NR | NR | 10 | NR | 0 | NR | NR | 11 |
| Renal involvement | NR | NR | 6 | NR | 0 | 10 | NR | NR |
| Complications and survival, % | | | | | | | | |
| Death | NR | 10 | 3 | 6 | 0 | 10 | 0 | 11 |
| Tracheostomy | 40 | NR | 5 | 6 | 42 | 10 | 14 | 3.5 |
| Tracheal collapse | NR | NR | NR | 14 | 42 | 0 | NR | NR |
| NR: Not Recorded | | | | | | | | |
RESULTS

Cumulative characteristics of previous large series are shown in Table 1 [2,5-10] and characteristics of our 8 patients are shown in Table 2.

Our cases included 5 men and 3 women, and the median age at diagnosis was 56.4 years (range 24 to 72). Three patients had associated rheumatoid arthritis, Sjögren’s syndrome, or ulcerative colitis.

In our series, the mean time from symptom onset to diagnosis was 9 months. One patient had been diagnosed as having bronchial asthma and ulcerative colitis for many years.

Four of 8 cases presented with auricular chondritis (Fig. 1a, case 4) and laryngotracheal involvement (Fig. 2, case 5 and Fig. 3, case 5). Three presented with a saddle nose deformity (Fig. 1b, case 3), and arthritis and ocular involvement were present in 2 cases. No patients had nasal chondritis, reduced hearing, or vestibular, skin, cardiac, vascular, nervous system, or renal involvement in our series.

Five cases underwent cartilage biopsy, and chondrolysis, chondritis, or perichondritis was detected in all cases. One case was autopsied. (Fig. 4, case 3) Antibody to type II collagen was positive in 5 of 6 cases. As this test was only performed once, we were not able to determine a correlation between disease activity and the anti-type II collagen antibody titer.

The diseases associated with RP are summarized in Table 3 [2,5,6,10]. Three cases had associated rheumatoid arthritis, ulcerative colitis, or Sjögren’s syndrome. Despite the small number of cases, the proportion with associated disease was higher than in previous reports.

All patients received prednisolone (5-15 mg/day) and 5 required immunosuppressive agents such as methotrexate (2 patients, 8 mg/week) and cyclosporine (3 patients, 75-125 mg/day). Two patients died of respiratory failure despite prednisolone and cyclosporine treatment. This was a greater proportion in a short duration than in previous reports (Table 4) [2,11].

### TABLE 2
Clinical characteristics of our patients

| Case number | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 |
|-------------|---|---|---|---|---|---|---|---|
| Demographic characteristics | | | | | | | | |
| Gender | F | F | M | M | M | F | F | F |
| Age at onset | 59 | 53 | 53 | 72 | 72 | 50 | 67 | 26 |
| Mean delay in diagnosis (month) | 1 | 6 | 1 | 3 | 12 | 46 | 2 | 1 |
| Smoking index (pack x years) | 300 | 150 | 800 | 0 | 700 | 30 | 0 | 10 |
| Associated disease | None | None | None | None | None | UC | RA | SJS |
| Clinical features | | | | | | | | |
| Auricular chondritis | + | + | + | + | + | - | + | + |
| Arthritis | + | - | - | - | - | - | + | + |
| Laryngotracheal involvement | + | - | + | + | + | + | + | - |
| Ocular involvement | - | + | + | - | - | - | - | - |
| Saddle nose | - | + | - | - | + | - | + | - |
| Skin involvement | - | - | - | - | - | - | - | + |
| Antibody to type II collagen | + | + | + | n.d | + | + | + | n.d |
| Biopsy | n.d | + | n.d | + | n.d | + | n.d | n.d |
| Treatment (mg) | PSL 8 | PSL 5 | mPSL 6 | PSL 5 | PSL 7.5 | PSL 5 | mPSL 8 | PSL 15 |
| Chest CT findings | | | | | | | | |
| Tracheal wall thickening | + | - | + | + | + | - | - | - |
| Tracheal wall calcification | + | + | + | - | - | + | + | - |
| Tracheal collapse | + | + | + | + | + | + | + | - |
| Death | alive | alive | dead | dead | alive | alive | alive | alive |

n.d: not done, UC: Ulcerative Colitis, RA: Rheumatoid Arthritis, SJS: Sjögren syndrome, PSL: Prednisolone, mPSL: Methylprednisolone, CsA: Cyclosporin A, MTX: Methotrexate
DISCUSSION

RP is very rare and is characterized by systemic destructive inflammatory lesions of cartilage. Uncertainty about presenting symptoms and episodes of RP may result in a significant delay in diagnosis. In addition, there is no specific laboratory marker for RP.

All of our patients were diagnosed using the McAdam or Damiani and Levine criteria [2,4]. Although 3 of 8 patients fulfilled the McAdam criteria, other cases required pathological examination. In our series, the number with ocular involvement was smaller than in other reports. However, cases with saddle nose deformity were common in our series. A saddle nose deformity was associated with poor prognosis in previous reports [5], as it may reflect longstanding disease. The presentation with saddle nose deformity in our cases may indicate late diagnosis of RP, failure to control disease activity, or rapid disease progression.

Dion et al. suggested that patients without hematologic or tracheobronchial involvement (about 65% of patients) had a good prognosis. According to another report, respiratory tract involvement affects 40%-56% of patients with RP and may involve any portion of the respiratory tree, including the distal bronchi [10]. Laryngotracheal involvement was common, especially in Japanese cases; one study found that 51% of RP cases are complicated by laryngotracheal involvement and some of these showed large airway collapse with respiratory failure [11]. Six of our 8 cases had laryngotracheal involvement, but the presenting symptom affected the respiratory tract in 3 of 8 cases. This may account for the deaths from respiratory failure. The 5-year survival rate in RP is reportedly 66-74%, with a 10-year survival rate of 55% [1,2,5,8]. However, the survival times were only 58 and 21 months after diagnosis in the 2 patients who died. One case had been diagnosed as having bronchial asthma and was only treated with inhaled corticosteroids and long-acting beta agonists. The other case had been treated with corticosteroids by an otolaryngologist for auricular chondritis, and pulmonary function testing or computed tomography (CT) had not been performed. Subsequent pulmonary function testing showed established intra- or extrathoracic upper airway obstruction and CT showed tracheal wall thickening with calcification. This indicated that chondritis of the tracheal cartilage had been uncontrolled. Missed diagnosis early in the course of disease led to airway destruction prior to presentation with respiratory symptoms and subsequent diagnosis of RP. Undiagnosed for a prolonged period, airway involvement can cause fibrosis of the tracheobronchial wall, leading to fixed stenosis. Eventually, this can progress to life-threatening airway collapse due to irreversible damage and loss of tissue integrity. RP should always be considered in the differential diagnosis of obstructive diseases.

About one-third of RP patients have associated collagen vascular disease, thyroid disease, or hematologic disorders [2,5,6,10]. Systemic vasculitis, rheumatoid arthritis, systemic lupus erythematosus, and Sjögren’s syndrome are more common in autoimmune

![Fig. 1. A: auricular swelling sparing the lobule. (case4), B: saddle-nose deformity (case 3)](image1)

![Fig. 2. Chest CT shows tracheal and bronchus wall thickening. (case 5)](image2)
Fig. 3. A: left middle bronchus, B: main trunchus, C: right middle bronchus. Bronchofiberscopy reveals edematous changes in the entire tracheobronchial tree. (case 5)

### TABLE 3.

Associated disease of relapsing polychondritis among our patients and previous reports

|                      | Our series | McAdam | Michet | Zeuner |
|----------------------|------------|--------|--------|--------|
| Year                 | 2017       | 1976   | 1986   | 1997   |
| Number of cases      | 8          | 159    | 112    | 62     |
| Rheumatoid Arthritis | 12.5%      | 4.7%   | 7.1%   | 11.3%  |
| Vasculitis           |            |         | 9.8%   |        |
| Systemic Lupus Erythematosus | 1.2% | 5.4% | 4.8% |
| Systemic Sclerosis   | 1.2%       |        |        |        |
| Sjogren Syndrome     | 12.5%      | 3.1%   |        |        |
| Ankylosing spondylitis| 3.2%      |        |        |        |
| Overlap Syndrome     |            | 1.8%   |        |        |
| Reiter's/Psoriatic Arthritis | 1.2% | 3.6% |        |
| Behcet disease       |            | 0.9%   |        |        |
| Polymyalgia rheumatica |          | 0.9%  |        |        |
| Primary biliary cholangitis |        | 0.9%  |        |        |
| Thyroid disease      | 4.7%       | 3.6%   | 3.2%   |        |
| Ulcerative colitis   | 12.5%      | 1.9%   | 3.2%   |        |
| Crohn's disease      |            |        |        | 1.6%   |
| Glomerulonephritis   | 1.2%       |        |        |        |
| Dysgammaglobulinemia | 1.2%       |        |        |        |
| Autoimmune hemolytic anemia | 0.6 |        | 1.6%   |        |
| Myelodysplastic syndromes |          | 5.4%  | 3.6%   |        |
| Idiopathic pulmonary fibrosis |          | 0.9%  | 1.6%   |        |
| Diabetes Mellitus    | 1.9%       |        | 1.6%   |        |
| Malignancy           | 3.1%       |        |        |        |
disease. No hematologic disorders were observed in our series, but associated hematologic malignancy and myelodysplastic syndrome always have a poor prognosis [10]. The possibility of associated RP must be considered when patients with respiratory symptoms also have an autoimmune disease.

All cases were treated with corticosteroid and immunosuppressive agents. However, 3 cases had received these drugs for associated disease. The primary treatment is systemic corticosteroid therapy. Prednisone is administered in the acute phase and requires low daily dose maintenance [1,2,4-11]. Other medications reported to control symptoms and disease progression include azathioprine, methotrexate, cyclophosphamide, and cyclosporine. Despite combined corticosteroid and immunosuppressive therapy, 2 cases experienced disease progression. The use of biological agents was recently reported, but their efficacy has not been established [12]. The availability of a marker of disease activity would make it easier to determine optimal treatment to prevent disease progression.

The limitations of this study are the small number of patients and bias due to recruitment in a small area. A larger series is needed to provide more insight into this condition in Japan.

CONCLUSION

We present a small series of 8 Japanese RP patients, with higher death and associated disease rates than in other reports. We believe that a delay in diagnosis contributed to the deaths in this series. Early diagnosis could result in better outcomes.

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![TABLE 4.](image)

|                      | Our series | McAdams | Michet | Oka |
|----------------------|------------|---------|--------|-----|
| Year                 | 2017       | 1976    | 1986   | 2010|
| Number of Cases      | 8          | 159     | 112    | 239 |
| Respiratory Failure  | 2          | 13      | 2      | 7   |
| COPD                 |            |         |        |     |
| Infection            | 4          | 12      | 4      |     |
| Cardiovascular       | 9          | 16      |        |     |
| Renal failure        | 2          |         |        |     |
| Malignancy           | 3          | 5       |        |     |
| Refractory anemia    |            |         | 1      |     |
| Gastric ulcer        |            |         |        | 1   |
| Unknown              | 8          |         | 11     |     |
| Total                | 2(25%)     | 37(23%) | 41(37%)| 22(9%)|

COPD: chronic obstructive lung disease
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