Original Article

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Clinical Characteristics of Relapsing Polychondritis: A Report of 8 Cases in Japan

MORIHIRO TAJIRI, MASAKI TOMINAGA, TAKASHI KINOSHITA, MASAYUKI NAKAMURA, SHINJIRO KAIEDA, MASAKI OKAMOTO, HIROAKI IDA, TOMOTAKA KAWAYAMA AND TOMOAKI HOSHINO

Division of Respirology, Neurology and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, Kurume 830-0011 Japan

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Summary: ***Objectives*:** Relapsing polychondritis (RP) is a very rare autoimmune disorder characterized by recurrent episodes of inflammation and destruction of cartilaginous tissues. We examined the clinical characteristics, management, and outcomes of Japanese RP patients.
***Methods*:** We identified 8 RP cases in our department between 2003 and 2017. Detailed clinical features, testing, treatment, and outcomes were recorded.
***Results*:** The mean time from symptom onset to diagnosis was 9 months. Four cases presented with auricular chondritis and laryngotracheal involvement and 3 cases presented with a saddle nose deformity. Anti-type Ⅱ collagen antibody was positive in 5 of 6 cases. Of 3 cases with associated diseases (rheumatoid arthritis, ulcerative colitis, and Sjögren's syndrome), 2 died of respiratory failure.
***Conclusions*:** When RP is diagnosed, early computed tomography or pulmonary function testing is essential to enable early treatment. Undiagnosed airway involvement can cause tracheobronchial wall fibrosis, leading to fixed stenosis.

Key words relapsing polychondritis, respiratory failure, laryngotracheal involvement

INTRODUCTION

Relapsing polychondritis (RP) is an uncommon autoimmune disease characterized by recurrent inflammation of cartilaginous hyaline, elastic, and fibrous 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.

Corresponding Author: Masaki Tominaga M.D., Ph.D., Division of Respirology, Neurology and Rheumatology, Department of Internal Medicine, Kurume University School of Medicine, 67 Asahi-machi, Kurume 830-0011, Japan. Tel: +81-942-31-7560, Fax: +81-942-31-7703, E-mail: tominaga_masaki@med.kurue-u.ac.jp

Abbreviations: CsA, Cyclosporine; mPSL, Methylprednisolone; MTX, Methotrexate; PSL, Prednisone; RA, Rheumatoid Arthritis; RP, Relapsing polychondritis; SJS, Sjogren syndrome; UC, Ulcerative Colitis.

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	Anan-thakrishna	Dion
Published Year	1976	1986	1997	1998	2003	2007	2009	2016
Number of cases	159	112	62	66	12	10	7	142
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	44	51	46.6	46	34	48.1	40.2	43.5
(range), year	NR	13-84	17-86	16-68	3-65	26-65	28-54	NR
Mean delay in diagnosis, month	NR	NR	NR	35	4.5	26	20	12
(range), month	NR	NR	NR	NR	0.5-36	NR	3-72	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

18012).

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								
uricular 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
Treatment (mg)	PSL 8 CsA 75	PSL 5	mPSL 6 CsA 75	PSL 5	PSL 7.5 MTX 8	PSL 5 CsA 125	mPSL 8 MTX 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: Sjogren syndrome, PSL: Prednisolone, mPSL: Methylprednisolone, CsA: Cyclosporin A, MTX: Methotrexate

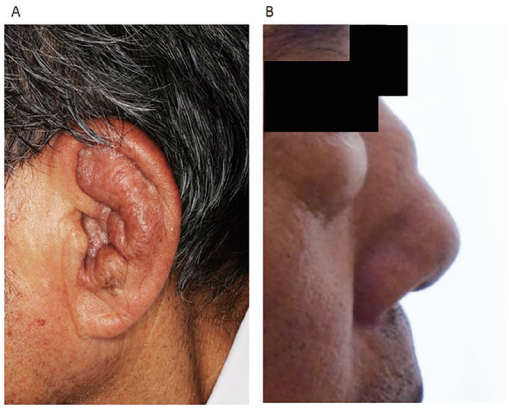

Fig. 1. A: auricular swelling sparing the lobule. (case4), B: saddle-nose deformity (case 3)

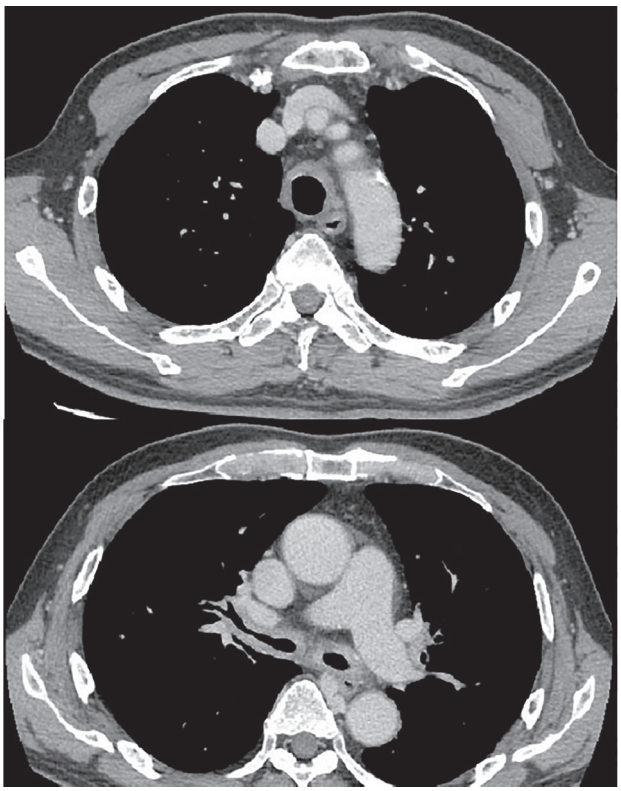

Fig. 2. Chest CT shows tracheal and bronchus wall thickening. (case 5)

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

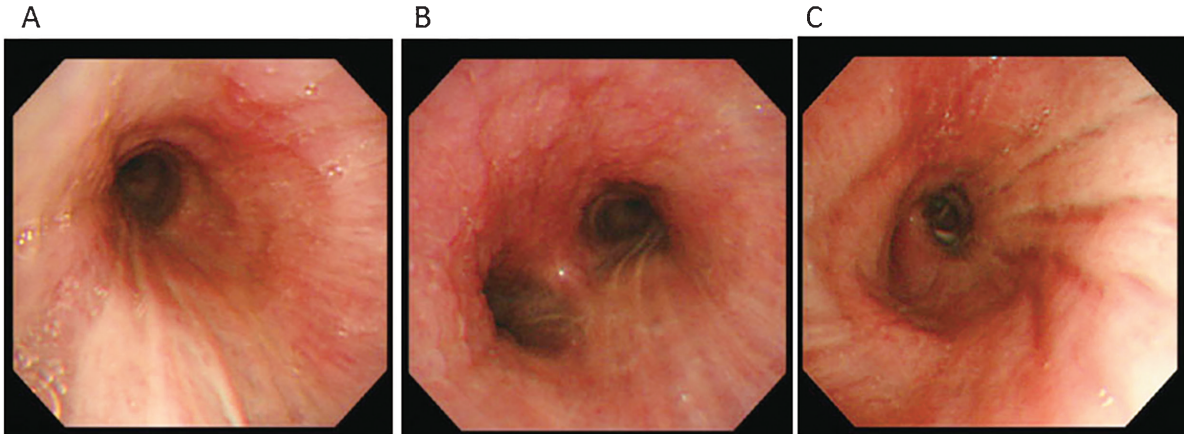

Fig. 3. A: left middle bronchus, B: main trunchus, C: right middle bronchus.
Bronchofiberscopy reveals edematous changes in the entire tracheobronchial tree. (case 5)

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	4.8
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		

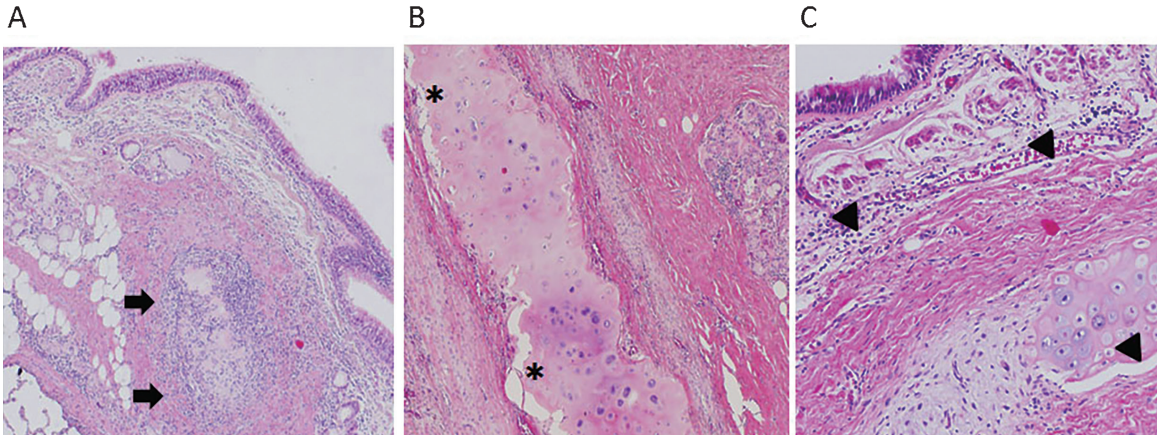

Fig. 4. Pathological findings of bronchus, they are obtained at autopsy (case 3).
A: A lot of inflammatory cells infiltrate around the cartilage (arrow). (HE ×40)
B: Cartilage demonstrates loss of normal basophilia (asterisk). (HE ×100)
C: Cartilage replaces to the fibrosis (arrow head). (HE ×100)

TABLE 4.
Cause of death with relapsing polychondritis among our patients and previous reports

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

COPD: chronic obstructive lung disease

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.

COMPETING INTERESTS: The authors have no conflicts of interest directly relevant to the content of this article.

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