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# Clinical analysis of relapsing polychondritis with airway involvement

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## Abstract

**Objective.** To identify the clinical characteristics, treatment, and prognosis of relapsing polychondritis patients with airway involvement.

**Methods.** Twenty-eight patients with relapsing polychondritis, hospitalised in the First Hospital of Shanxi Medical University between April 2011 and April 2021, were retrospectively analysed.

**Results.** Fifty per cent of relapsing polychondritis patients with airway involvement had a lower risk of ear and ocular involvement. Relapsing polychondritis patients with airway involvement had a longer time-to-diagnosis ($p < 0.001$), a poorer outcome following glucocorticoid combined with immunosuppressant treatment ($p = 0.004$), and a higher recurrence rate than those without airway involvement ($p = 0.004$). The rates of positive findings on chest computed tomography and bronchoscopy in relapsing polychondritis patients with airway involvement were 88.9 per cent and 85.7 per cent, respectively. Laryngoscopy analysis showed that 66.7 per cent of relapsing polychondritis patients had varying degrees of mucosal lesions.

**Conclusion.** For relapsing polychondritis patients with airway involvement, drug treatment should be combined with local airway management.

## Main Article

Dr S-X Wen takes responsibility for the integrity of the content of the paper

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## Introduction

As a rare multi-systemic autoimmune disease,[1] relapsing polychondritis is characterised by recurrent inflammation and progressive damage to cartilage at the lesion site. Relapsing polychondritis mainly afflicts systemic cartilage and proteoglycan-rich tissues. There are high rates of misdiagnosis and missed diagnosis in relapsing polychondritis patients with airway involvement. Irreversible damage to the tracheal cartilage can result in tracheal collapse and treatment failure, which complicates airway treatment, increases the financial burden on the patient, and may lead to death.[2]

Tremendous advancements have been accomplished in the diagnosis and treatment of relapsing polychondritis. However, a comprehensive clinical comparison has not been performed on relapsing polychondritis patients with or without airway involvement. This research compared the clinical characteristics, diagnosis and treatment of relapsing polychondritis patients with and without airway involvement. The findings obtained in the current study form a crucial clinical basis for the diagnosis and treatment of relapsing polychondritis.

## Materials and methods

### *Patients*

This study comprised 28 in-patients (16 males and 12 females) diagnosed with relapsing polychondritis at the First Hospital of Shanxi Medical University between April 2011 and April 2021. The mean age of onset of relapsing polychondritis was 45 ± 15 years, ranging from 18 to 68 years. Further examination showed that 14 patients presented with airway involvement.

### *Diagnostic criteria*

The diagnostic criteria for relapsing polychondritis by Damiani and Levine[3] are as follows: (1) patients meeting three or more of the McAdam *et al.*[4] criteria (i.e. recurrent bilateral auricular chondritis; non-erosive inflammatory polyarthritis; nasal chondritis; inflammation of ocular structures; chondritis of the respiratory tract; and cochlear and/or vestibular damage); (2) patients meeting one of six of McAdam *et al.* criteria, with a positive histological confirmation; and (3) patients matching two of six of McAdam *et al.* criteria, and who respond to corticosteroids or dapsone (satisfying any of

these criteria). Patients who met one or more of the preceding criteria were classified as relapsing polychondritis patients.[5]

Relapsing polychondritis with airway involvement was defined as follows: (1) patients meeting the diagnostic criteria of Damiani and Levine; (2) patients with airway involvement symptoms at the time of disease onset or progression, and patients without relevant symptoms but with laryngeal or tracheobronchial cartilage involvement as revealed by computed tomography (CT) examination; and (3) patients without laryngeal tumours, tracheobronchial tumours, bronchial asthma, laryngeal amyloidosis, laryngeal or tracheobronchial tuberculosis, or granulomatosis with polyangiitis.

### Treatment

Patients in both groups (with or without airway involvement) received glucocorticoid (30–40 mg/day) in combination with immunosuppressive drugs (methotrexate, cyclosporine or cyclophosphamide). When the aforesaid treatment options failed, biological medication or surgical treatment was utilised as a supplement.

### Statistical analysis

Statistical analysis was performed using SPSS® software version 21.0. Categorical data were expressed as percentages, and were compared using Fisher's exact test or the rank-sum test. Continuous data conforming to normal distribution were expressed as mean ± standard deviation values, and analysed using the independent sample *t*-test. Non-normally distributed data were presented as interquartile ranges and compared using the non-parametric rank-sum test. All statistical tests were two-sided, and the significance level was set at a *p*-value of less than 0.05.

## Results

### Clinical characteristics

Table 1 displays the information on patients' age and gender. The findings depicted no statistically significant differences between the two groups in terms of demographic characteristics.

Clinical examination demonstrated that 12 of the 28 relapsing polychondritis patients presented with ear involvement at the time of disease onset. Additionally, 15 relapsing polychondritis patients developed ear involvement during disease progression. Airway involvement occurred in 10 relapsing polychondritis patients, and airway involvement symptoms developed in 14 relapsing polychondritis patients during disease progression. There were 2 relapsing polychondritis patients with ocular inflammation at the time of disease onset, and 11 relapsing polychondritis patients developing ocular inflammation as the disease progressed. Nasal cartilage inflammation was observed in one relapsing polychondritis patient, while collapsed or swollen nasal cartilage was noted in six relapsing polychondritis patients. Our data suggested two cases of airway involvement including ear involvement, two cases with eye involvement, and five with nasal involvement.

### Comparisons of treatment and prognosis

The symptoms of 13 relapsing polychondritis patients (8 patients with the airway intact and 5 patients with airway involvement) were managed with glucocorticoids combined with immunosuppressants. The results revealed that patients in the two groups underwent significantly different treatment modalities. Additionally, relapsing polychondritis patients with airway involvement had a higher re-hospitalisation rate because of recurrence than those without airway involvement (Table 1).

## Discussion

Relapsing polychondritis is a rare autoimmune disease that influences both males and females,[6] but has a higher prevalence in middle-aged individuals. Our research included 16 males and 12 females, with age of disease onset ranging from 18 to 68 years. No obvious differences were observed between patients with and without airway involvement regarding gender and age.

The annual incidence of relapsing polychondritis ranges from 0.71 to 3.5 per million people,[4] and 18–26 per cent of relapsing polychondritis patients present with respiratory involvement.[7] Approximately half of relapsing polychondritis patients experience different degrees of airway involvement during disease progression.[8] A retrospective analysis of 142 relapsing polychondritis patients in France found that 43 per cent of the patients had laryngeal involvement and 22 per cent had tracheal involvement.[9] Furthermore, a retrospective analysis of 239 patients found that airway involvement occurred in 50 per cent of relapsing polychondritis patients.[10] Two large-sample studies conducted in China reported that approximately 69–81.7 per cent of relapsing polychondritis patients had airway involvement.[11,12] Wang *et al.* performed a prospective study, and reported that approximately 81.5 per cent of relapsing polychondritis patients had airway involvement.[13]

In the current study, a retrospective case comparative analysis was conducted, and the findings revealed that patients with airway involvement accounted for 50 per cent of all relapsing polychondritis patients. Of note, the clinical misdiagnosis rate for relapsing polychondritis patients with airway involvement was high, at 85.7 per cent, suggesting a high incidence of relapsing polychondritis patients with airway involvement. However, laboratory and pathological auxiliary examinations are ineffective for diagnosis, as atypical clinical symptoms contribute to a high rate of misdiagnosis.

Clinical typing of relapsing polychondritis is critical to improve diagnostic rates. A previous study categorised relapsing polychondritis into three types based on the affected sites: 'R' type, characterised by airway involvement; 'A' type, characterised by ear involvement; and 'O' type, characterised by airway and ear involvement. These types were analysed, and it was discovered that there were conspicuous differences in the incidence, clinical diagnosis and treatment of patients with different types of relapsing polychondritis.[10] Additionally, a French study revealed that although airway involvement is the major cause of death in relapsing polychondritis patients, airway involvement is not highly correlated with heart involvement.[9] Research conducted in China classified relapsing polychondritis into four types based on the affected organs, as follows: 'A' type, characterised by airway involvement; 'B' type, characterised by ear involvement; 'C' type, characterised by overlapping involvements; and 'D' type, in which the airway and ear are unaffected. The results revealed noticeable differences in the clinical diagnosis and prognosis among the types. Patients with subtype A relapsing polychondritis had a greater risk of nasal cartilage

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**Table 1.** Comparisons of clinical characteristics between relapsing polychondritis patients with or without airway involvement

| Characteristic | RP patients with airway involvement (*n* (%)) | RP patients without airway involvement (*n* (%)) | Total (*n*) | *P*-value |
|---|---|---|---|---|
| Gender | | | | NS |
| – Male | 7 (43.75) | 9 (56.25) | 16 | |
| – Female | 7 (58.3) | 5 (41.7) | 12 | |
| Age at diagnosis | | | | NS |
| – <18 years | 0 (0) | 0 (0) | 0 | |
| – 18–65 years | 12 (48) | 13 (52) | 25 | |
| – ≥66 years | 2 (66.7) | 1 (33.3) | 3 | |
| Ear involvement | 2 (13.3) | 13 (86.7) | 15 | <0.001 |
| Nose involvement | 5 (83.3) | 1 (16.7) | 6 | NS |
| Ocular involvement | 2 (18.2) | 9 (81.8) | 11 | 0.018 |
| Misdiagnosis | 12 (60) | 8 (40) | 20 | NS |
| Glucocorticoid + immunosuppressant administration | | | | |
| – Controlled | 5 (22.8) | 13 (72.2) | 18 | 0.004 |
| – Uncontrolled | 9 (90) | 1 (10) | 10 | |
| Number of re-hospitalisations | | | | |
| – >5 times | 6 (85.7) | 1 (14.3) | 7 | |
| – 3–5 times | 8 (57.1) | 6 (42.9) | 14 | 0.004 |
| – <3 times | 0 (0) | 7 (100) | 7 | |

RP = relapsing polychondritis; NS = not significant

**Table 2.** Comparison of time-to-diagnosis between relapsing polychondritis patients with or without airway involvement

| Parameter | RP patients with airway involvement | RP patients without airway involvement | Z | *P*-value |
|---|---|---|---|---|
| Time-to-diagnosis (median (25%, 75%); days) | 120 (90.365) | 30 (13.180) | −20.36 | <0.001 |

RP = relapsing polychondritis; SD = standard deviation

involvement, and those with subtype B disease had a higher risk of eye involvement and a better prognosis than patients with the other subtypes.[14]

In this study, relapsing polychondritis patients were assigned to two groups based on the presence or absence of airway involvement. Patients with airway involvement were less likely to develop ear and eye involvement than those without airway involvement. Additionally, airway involvement was difficult to diagnose, with higher rates of misdiagnosis and missed diagnosis in this group, triggering a protracted disease course, increased re-hospitalisation rates and a poor prognosis (Tables 1 and 2).

Airway involvement is the main risk factor for death in relapsing polychondritis patients.[15] Early and timely diagnosis and treatment can substantially improve the prognosis of relapsing polychondritis patients with airway involvement.[13] However, the existing diagnostic criteria are mainly based on the clinical characteristics of patients, and are ineffective for the early diagnosis of relapsing polychondritis. Prior reports revealed that additional investigations, such as CT and endoscopy of the neck and chest, can be applied for the early diagnosis and differential diagnosis of relapsing polychondritis.[16–18] In our study, the rate of positive chest CT examination findings, namely varying degrees of airway thickening, stenosis and calcification, was 88.9 per cent in airway-affected patients. The predominant symptom was thickening of the main bronchial wall, which is concordant with the findings of Wang *et al.*[13] Bronchoscopy exhibited findings that were positive for airway involvement in 85.7 per cent of patients. The findings demonstrated varying degrees of tracheal mucosal thickening, stenosis and oedema in relapsing polychondritis patients. Multiple mucosal lesions appeared in 66.7 per cent of patients, as determined by laryngoscopy analysis. In patients with laryngeal involvement, the neck CT results were concurrent with the laryngoscopy results.

Prior studies have shown that $^{18}$F-fluoro-2-deoxyglucose positron emission tomography (FDG-PET)/CT images exhibited the characteristic features of relapsing polychondritis.[19,20] Chen *et al.* conducted a review of 28 relapsing polychondritis patients with airway involvement, all of whom underwent PET/CT examination.[21] Twenty-four PET/CT scans of the tracheal and bronchial trachea revealed augmented density, tube wall oedema, thickening and calcification, and limited stenosis. Furthermore, four patients had increased density and tube wall thickening, and oedema in laryngeal cartilage. Intriguingly, PET/CT assumes a pivotal role in guiding biopsy, because of the high metabolic rate at the affected site. Biopsy performed at sites with hypermetabolic activity according to PET/CT was associated with positive results in 93.3 per cent of cases, illustrating that this imaging is effective for the diagnosis of relapsing polychondritis.[22] In our study, one patient was

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diagnosed with relapsing polychondritis following PET-CT examination. However, the role of PET-CT in the diagnosis and prognosis of relapsing polychondritis should be further explored.

The findings showed that glucocorticoids and immunosuppressants were ineffective in relapsing polychondritis patients with airway involvement, emphasising that early pharmacological management is necessary to prevent relapsing polychondritis progression. Patients with dyspnoea should have their treatment plans adjusted to their condition, and effective surgical intervention should be implemented when appropriate.[23]

At present, tracheostomy and endotracheal stent implantation are the only surgical options for the short-term relief of dyspnoea. Oryoji *et al.*[24] successfully resuscitated a 73-year-old man who had suffered acute respiratory failure due to relapsing polychondritis with airway involvement, through metal stent implantation and tracheostomy. In the present study, five patients underwent a tracheostomy in addition to receiving glucocorticoid and immunosuppressants; effective airway management was achieved in four of these patients.

Stent placement is prone to complications such as stent fracture, pulmonary artery or airway erosion, bleeding, or granulation tissue ingrowth.[25] In light of this, and because complications including respiratory infection and airway obstruction usually occur four to six weeks following surgery, some scholars suggest an initial review period of two to four weeks, followed by review every three months.[26] In a study by Guo *et al.*,[23] a patient implanted with membrane-covered stents for half a year developed extensive granulation tissue growth and mucosal destruction, as observed at follow up, necessitating removal of the stents. In this study, one patient with central airway involvement suffered granulation tissue hyperplasia at the stent – a post-stenting complication; this patient eventually died after developing pulmonary infection and dyspnoea.

For long-term treatment, the surgical treatment regimens include: tracheobronchial external fixation, laryngeal tracheal reconstruction, tracheal sleeve resection, and balloon dilatation with adjustable pressure and security performance.[24,27,28] Tracheobronchial external fixation, in which the collapsed trachea is sutured and suspended over autologous tissues or grafts to open the airway, is suitable for patients with extensive airway softening and collapse. Laryngeal tracheal reconstruction is indicated for patients with limited stenosis of the trachea or subglottis. It utilises a sternocleidomastoid muscle flap or costal cartilage to broaden the laryngeal tracheal reconstruction. Xie *et al.*[28] reported a successful tracheal restoration using thymus lingual muscle, in a patient with laryngeal stenosis induced by relapsing polychondritis. Tracheal sleeve resection, which is suitable for limited airway stenosis, requires long-term drug treatment and a T-type tube following surgery. Balloon dilatation with adjustable pressure and security performance is suitable for relapsing polychondritis induced laryngeal and tracheal stenosis.

One retrospective study enrolled 11 patients with different degrees of airway stenosis caused by relapsing polychondritis, in which: 9 patients underwent laryngotracheal reconstruction surgery with a sternohyoid myocutaneous flap or costal cartilage to widen laryngeal tracheal reconstruction, 1 patient underwent long-term T-tube placement, and 1 patient underwent routine balloon dilatation. All patients had complete recovery of respiratory and swallowing functions after two to seven years.[23]

In addition to the surgery itself, we should calm patients' emotions prior to treatment, administer anaesthesia, and adequately absorb and discharge sputum, all of which should be supported by hormone therapy pre- and post-operatively.

Biological medication has revolutionised the management of refractory relapsing polychondritis. For instance, tumour necrosis factor-α and interleukin-6 receptor antagonists are effective in the treatment of relapsing polychondritis cases.[29] However, randomised double-blind experiments with large samples are required to verify their effectiveness. In the current study, two patients received adalimumab injections; the results indicated that this treatment was effective in one patient. Bronchial involvement causes diffuse airway stenosis in patients, with the majority of these lesions occurring in the thoracic segment, for which nasal positive pressure ventilation is recommended.[30] Patients who require urgent surgical treatment should be counselled before treatment and administered adequate anaesthesia. Additionally, complete sputum suction and hormone treatment may be employed as adjunctive therapies.

- In relapsing polychondritis with airway involvement, misdiagnosis and missed diagnosis rates rise, resulting in longer time-to-diagnosis, more re-admissions and worse outcomes
- Despite diagnosis and treatment advances, there is no specific examination, making clinical diagnosis problematic, and medication remains the mainstay of therapeutic care
- This study evaluated clinical features, therapeutic choices and prognosis of relapsing polychondritis patients with airway involvement
- Computed tomography and endoscopy are excellent clinical diagnostic tools for relapsing polychondritis patients with airway involvement
- To enhance prognosis, relapsing polychondritis patients should receive tailored therapeutic treatments; drug therapy should be used in conjunction with local airway control

## Conclusion

The findings demonstrated that 50 per cent of relapsing polychondritis patients presented with airway involvement as the disease progressed. However, owing to the lack of specific examination methods and poor awareness of the disease, the clinical misdiagnosis rate was high (85.7 per cent). Clinical diagnostic and treatment outcomes for relapsing polychondritis patients were markedly different between the airway-affected and airway-unaffected subgroups. These findings suggest that relapsing polychondritis patients should undergo an individualised therapeutic regimen and be reviewed regularly to improve their prognosis.

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**Competing interests.** None declared

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