Clinical patterns and the evolution of relapsing polychondritis based on organ involvement: a Chinese retrospective cohort study

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Research

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Abstract

Background

Relapsing polychondritis(RPC) is a rare autoimmune disease, of which the diagnosis in early stage is challenging. Defining the clinical patterns and disease evolution may help early recognition of this rare disease.

Results

Sixty-six males and 60 females were included with onset age of 47.1 ± 13.8 years and followed up for a median of 18 months. Correlation analysis revealed a strong negative correlation between airway involvement and auricular chondritis ($r = -0.75$, $P < 0.001$). Four distinct clinical patterns were identified: Ear pattern (50.8%), Airway pattern (38.9%), Overlap pattern (4.8%) and Airway-Ear negative pattern (5.6%) and patients with Ear pattern and Airway pattern were subdivided as limited and systemic form of RPC (27.8% with limited form of Ear pattern and 24.6% with limited form of Airway pattern). During follow-up, a small part of patients with Ear pattern and Airway pattern progressed into Overlap pattern and some Airway-Ear negative pattern patients progressed into Ear pattern. Most of the limited RPC patients remained limited form during follow-up while some patients with limited form progressed into systemic form. Patients with Ear pattern had the highest survival rate and relative lower inflammatory status.

Conclusions

RPC patients can be categorized as 4 different clinical patterns and 2 distinct presenting forms (limited and systemic) based on organ involvement, and clinical patterns and presenting forms can evolve during follow-up. Our findings may facilitate early recognition of this rare disease and contribute to an updated classification criteria covering all the clinical spectrum of RPC

Background

Relapsing Polychondritis (RPC) is a systemic inflammatory disorder of unknown etiology and characterized by recurrent and progressive inflammation of the cartilaginous structures, particularly involving the auricles, nose and respiratory tract, as well as extra-cartilaginous tissues, including eyes, heart, skin, central nervous and hematological systems[1-3].

The incidence of RPC was estimated to be 3.5 per million per year in the U.S. [4]and 0.71 per million population per year between 1990 and 2012 in the UK[5]. Patients may visit physicians at different departments, mainly non-rheumatologic specialists[5-8], due to protean manifestations and wax and wane disease courses of RPC, and often experience a misdiagnosis[6-8], leading to delayed diagnosis[5-13].

Because of the rarity of the disease, the diagnosis is mainly based on traditional criteria empirically proposed by McAdams et al.[14] or Damiani et al. [15] and Michet et al.[16]. However, these criteria easily miss patients at early stage because of the inadequacy of clinical manifestations[8]. Meanwhile, partial RPC has been reported by Mathew et al. [11] and our previous study[6], and limited RPC is not uncommon in clinical settings as demonstrated by our previous study [6] and case reports [17-24]. As a result, these patients do not meet with the current criteria. Furthermore, the insufficient disease awareness of physicians, especially of non-rheumatologic specialists, at least partially contributes to diagnostic delay and misdiagnosis[6, 25, 26]. Thus, clinical pattern analysis of RPC patients, especially of patients in early stage as well as partial and limited RPC, may assist clinicians to bear a comprehensive disease picture in mind, which subsequently may help to improve diagnostic strategy. Although Dion et al.[27] and Shimizu et al.[28, 29] have made such attempts, however, these two studies did not cover all clinical spectrum of this disease because they included neither RPC patients in early stage nor partial or limited RPC patients. Therefore, we conducted this study aiming at defining distinct clinical patterns based on organ involvement using our own cohort which included early-stage RPC patients as well as partial and limited RPC patients. In addition, we described the evolution of clinical patterns for the first time.

Results

Patient characteristics.

The current study included 66 male and 60 female patients with age of 47.1 ± 13.8 years at disease onset. The age of male patients was comparable to female patients at disease onset (46.1 ± 13.7 vs 48.1 ± 13.8 , $P=0.408$). Median duration of follow-up after diagnosis was 18 months (range 1-153 months), with 34 patients followed up for at least 36 months, 51 patients for at least 24 months and 82 patients for at least 12 months. One patient with airway involvement was lost after 2 months follow-up. Median disease duration since disease onset was 26 months (range 3-162 months). Median diagnostic delay was 5 months (range 0-132 months), and 31 patients were delayed for over a year.

Initial and Cumulative Features

The most frequent initial features included auricular chondritis ($n=70, 55.6\%$) and airway involvement ($n=54, 42.9\%$) (including 17 patients[13.5%] with laryngeal involvement and 48 patients[38.1%] with tracheobronchial involvement), ocular inflammation ($n=25, 19.8\%$), fever ($n=20, 15.9\%$), nasal chondritis ($n=15, 14.3\%$), arthritis ($n=16, 12.7\%$), hearing loss ($n=12, 9.5\%$), cardiac involvement ($n=8, 6.3\%$), costochondritis ($n=3, 2.4\%$), neurological involvement ($n=6, 4.8\%$), cutaneous manifestations ($n=1, 0.8\%$), and myelodysplastic syndrome ($n=1, 0.8\%$). More cumulative features developed during follow-up, which were detailed in Table 1 as well as cumulative features in previous reports [7-9, 11, 13, 14, 16, 27, 31, 32].

At the last follow-up, airway involvement was found in 60 patients (47.7%), among them, 19 patients (15.1%) presented with laryngeal involvement and 51 patients (40.5%) with tracheobronchial involvement, indicating 10 patients with both laryngeal and tracheobronchial involvement (Table 1).

Neurological involvement was seen in 6 patients (4.8%), and no new onset of neurological impairment was observed during follow-up. One patient with rupture of intracranial aneurysm (anterior communicating artery) received surgical procedures. Four patients presented psychiatric symptoms, and 1 patient with headache and diplopia, and the Magnetic Resonance Imaging (MRI) of these 5 patients revealed ischemia and edema of the brain in 4 patients and demyelination in 1 patient, and the lesions were detected in frontal and parietal cerebrum as well as basal ganglia, unilaterally or bilaterally. Cerebrospinal fluid tests of the latter 5 patients were normal in 4 patients and increased white blood cells (mainly neutrophils initially) in 1 patient. The cerebrospinal fluid pressure was increased in 2 patients and normal in 3 patients. Cardiac involvement was found in 13 patients (10.3%), including premature contraction in 8, atrial tachycardia in 2, conduction block in 2, atrial fibrillation in 2, valve insufficiency in 1 and pre-excitation syndrome in 1.

Associated autoimmune conditions were found in 4 patients, including 2 patients with recurrent oral ulceration, 1 patient with Sjögren's syndrome and 1 patient with IgG4 associated periorbital pseudo-tumor.

Clinical pattern and disease evolution

We performed correlation analysis and calculated correlation coefficients between cumulative organ involvement and found a strong negative correlation between airway involvement and auricular chondritis ($r=-0.75$, $P<0.001$) and between tracheobronchial involvement and auricular chondritis ($r=-0.74$, $P<0.001$). A weak negative correlation was found between laryngeal involvement and auricular chondritis ($r=-0.24$, $P=0.007$).

We also found weak negative correlation between ocular inflammation and tracheobronchial involvement ($r=-0.32$, $P<0.001$), between arthritis and tracheobronchial involvement ($r=-0.26$, $P=0.003$), as well as between auricular involvement and nasal chondritis ($r=-0.20$, $P=0.028$). Weak positive correlation was found between hearing loss and nasal chondritis ($r=0.36$, $P<0.001$), hearing loss and cardiac involvement ($r=0.28$, $P=0.002$), nasal chondritis and tracheobronchial involvement ($r=0.20$, $P=0.021$), ocular inflammation and arthritis ($r=0.361$, $P<0.001$), nasal involvement and myelodysplasia ($r=0.20$, $P=0.025$) as well as cardiac involvement and myelodysplasia ($r=0.26$, $P=0.003$). Figure 1 shows the relationship between different organ involvement.

Based on these findings, 4 clinical patterns were identified: Ear pattern (ear involved but no airway involvement, subgroup A), Airway pattern (airway involved but no ear involvement, subgroup B), Overlap pattern (both ear and airway involved, subgroup C) and Airway-Ear negative pattern (neither auricular nor airway involved, subgroup D), which were detailed in Table 2. Apparently, Ear pattern and Airway pattern constituted the most part of RPC patients (50.8% and 38.9% for Ear pattern and Airway pattern respectively at disease onset and 49.2% and 38.1% for Ear pattern and Airway pattern respectively during follow-up).

A proportion of patients with Ear pattern and Airway pattern presented with auricular chondritis and airway involvement as the sole manifestation at disease onset and during disease course, and were classified as limited RPC and the rest were classified as systemic RPC (Table 2).

After that, we analyzed the evolution of the clinical patterns from disease onset to the last visit, as detailed in Figure 2. The evolution can be summarized as follows. First, one clinical pattern can progress into another clinical pattern. Six patients with Ear pattern (3 limited form and 3 systemic form) developed airway lesions and one patient with Airway pattern developed auricular chondritis and thus they progressed into Overlap pattern. Four patients with Airway-Ear negative pattern developed auricular chondritis and progressed into Ear pattern. Second, limited RPC can progress into systemic RPC. Seven limited RPC patients with Ear pattern and 5 limited RPC patients with Airway pattern progressed into systemic disease. Third, most of the limited RPC patients (25 with Ear pattern and 26 with airway pattern) remained limited form during follow-up, indicating no disease progression in these patients.

Clinical features compared between different patterns

Compared with those with Airway pattern, RPC patients with Ear pattern presented with higher incidence of ocular involvement (38.7% vs 8.3%, $P<0.001$) and arthritis (27.4% vs 4.2%, $P=0.002$) but relative lower incidence of nasal chondritis (6.5% vs 25%, $P=0.011$). Importantly, RPC patients with Airway pattern had higher mortality rate compared with those with Ear pattern (29.2% vs 1.6%, $P=0.015$). Interestingly, Overlap pattern seems to be a combination of Ear pattern and Airway pattern, since RPC patients with Overlap pattern presented intermediate incidence rate of ocular involvement (23.1%) and arthritis (15.4%) and mortality rate (23.1%) between that of those with Ear pattern and Airway pattern, but relatively higher incidence of hearing loss (23.1%) and nasal chondritis (30.8%) compared to those with Ear pattern and Airway pattern (Table 3). Among 3 Airway-Ear negative pattern patients, all presented with ocular involvement and 2 presented with hearing loss, nasal chondritis, and arthritis respectively. No significant difference of age at disease onset was detected between different patterns but Ear pattern presented lower CRP level compared with Airway pattern and Overlap pattern, indicating lower inflammation of RPC patients with Ear pattern (Table 3).

There were 18 deaths (14.3%) during a median follow-up of 23.5 months (range 5-81 months), and the causes of deaths were refractory disease ($n=13$), pulmonary infection ($n=3$), brain tumor ($n=1$), and unknown cause ($n=1$), 1 with ear pattern (died of brain tumor), 14 with airway pattern and 3 with overlap pattern.

The probability of survival was significantly different between Ear pattern and the other 2 patterns whereas no difference existed between Airway pattern and Overlap pattern (Figure 3). This indicates that airway involvement may be a predominant factor associated with poor prognosis.

Discussion

The diagnosis of RPC in early stage remains challenging since the first description in 1932, even after the introduction of empirical diagnostic criteria by McAdams [14] or Damiani et al. [15] and Michet et al. [16]. Due to lack of the development of new criteria aiming for early diagnosis, being aware of clinical patterns and disease evolution may help clinicians to diagnose this rare disease in early stage. Herein, we report a retrospective cohort of 126 Chinese RPC patients with definition of 4 clinical patterns and 2 presenting forms (limited and systemic forms) and described the evolution of clinical patterns during follow-up.

Cumulative features of large case series were summarized in Table 1 and most series were about Caucasians. Patients from different regions may manifest with distinct features. The age at diagnosis of our patients was comparable to previous reports. The diagnostic delay was much shorter than previous study, indicating more RPC patients in early stage were included in our study. Comparable airway involvement but lower frequency of other features were observed, which may be due to the shorter follow-up period of our study. Meanwhile, it also demonstrated relatively more severe disease in Chinese population, since more patients in our cohort developed airway involvement in a relatively short follow-up duration compared with other reports. In concordance with Lin's findings [7], the patients in our study had a higher initial frequency of laryngo-tracheal involvement (42.9%) than the Caucasians (14-38% initially), again demonstrating more severe disease in Chinese population, consistent with the observations made by Kong et al. [33].

Clinical classification is of vital importance to for early diagnosis. Although Dion et al.[27] and Shimizu et al.[28, 29] have made such attempts, however, these two studies did not cover all clinical spectrum of this disease. The French study by Dion et al. [27] classified the disease into three clinical subtypes: hematologic (with the worst prognosis), respiratory and mild phenotype. However, hematologic involvement constitutes a relative larger part in this cohort (8% had MDS and 13% had hematologic diseases) than that in Chinese patients (only 3.2% in our cohort and 0 in Lin's cohort had MDS), indicating that this classification may not be suitable for Chinese patients. In addition, this classification seems not to be developed for early diagnosis since this classification was based on disease severity, progression and prognosis instead of the initial presentations. Correlation analysis of 239 cases by Shimizu et al. [28] showed that a strong negative correlation exists between airway involvement and external ear involvement ($r=-0.48$). Therefore, the disease was divided into three clinical subgroups[29]: airway involvement (47 cases), external ear involvement (118 cases) and both airway and external ear involvement (70 cases). However, this study did not include limited RPC and partial RPC. The re-analysis of the cohort data by French scholars also found a negative correlation between tracheobronchial involvement and external ear involvement ($r=-0.245$, $P=0.003$) but not the airway overall [34].

By correlation analysis, however, our current study demonstrated a much stronger negative correlation between airway involvement and auricular chondritis ($r=-0.754$, $P<0.001$) than that of Japanese and French studies by Shimizu et al [28, 29] and Dion et al. [34]. Based on these findings, we divided RPC patients into 4 clinical patterns: Ear pattern (Subgroup A), Airway pattern (Subgroup B), Overlap pattern (Subgroup C) and Airway-Ear negative pattern (Subgroup D). The fact that patients with Ear pattern had the best prognosis and relative lower inflammatory status further suggests that patients with ear involvement can be a distinct clinical pattern. Ear pattern and Airway pattern had the largest number of patients, while Overlap pattern and Airway-Ear negative pattern had a relatively small number of patients. However, the clinical pattern did not remain unchanged during follow-up. Ear pattern and Airway pattern may progress into Overlap pattern and Airway-Ear negative pattern may progress into ear pattern while limited form may progress into systemic form, which reflected the progression of the disease. Particular attention should be paid to that a small number of patients with Ear pattern can progress into Overlap pattern, indicating a severe progression leading to disastrous consequences. The analysis of clinical characteristics of different patterns indicated the relationship between auricular chondritis and ocular inflammation and arthritis, and relationship between airway involvement and nasal chondritis, which reflect different disease pathogenesis between different clinical patterns.

Patients with laryngo-tracheal manifestation or auricular inflammation as the only initial feature of the disease[13], sometimes as the sole feature [8, 17-24], have been defined as limited form of RPC. In our cohort, 47.6% of the patients presented as limited RPC initially and 45.2% remained limited form during follow-up, suggesting that the limited RPC is not uncommon among Chinese patients. The concept of limited and systemic form is also supported by a recent online survey conducted by US authors[8] but with much lower incidence of limited RPC (16 and 2 out of 304 patients presented as isolated ear involvement and isolated airway involvement respectively).

There are some limitations of our study. First, the retrospective analysis of the hospitalized patients can miss some out-clinic patients causing incomplete inclusion of clinical features. Second, the relatively short follow-up duration may underestimate the frequency of organ involvements. But our study also has some strengths. First, we include RPC patients in early stage

because the diagnostic delay was much shorter than previous study which may facilitate early recognition of RPC. Second, we included full spectrum of this rare disease because a proportion of our patients presented as partial RPC and limited RPC, which further strengthen the consensus that new classification criteria should be put on agenda.

Conclusions

In conclusion, our study included early RPC patients, defined distinct characteristics of Chinese RPC patients and categorized them into 4 different clinical patterns and 2 distinct presenting forms (limited and systemic forms) which may facilitate early recognition of this rare disease. In addition, we believe our study may contribute to an updated classification criteria covering all the clinical spectrum of RPC.

Abbreviations

RPC
relapsing polychondritis; ANCA:anti-neutrophilic cytoplasmic antibody; CRP:C-reactive protein

Methods

Study population

We retrospectively reviewed the medical records of 126 RPC patients that were hospitalized and followed-up by rheumatologists at our hospital between January, 2008 and August, 2019. RPC was defined according to traditional criteria proposed by Michet et al.[16] and Damiani et al.[15]. Patients that underwent recurrent chondritis associated with deformity, in accompany with vestibular dysfunction, ocular inflammation, or inflammatory arthritis were diagnosed as partial RPC as suggested by Mathew et al. [11]. Limited RPC can also be diagnosed if patients presented with recurrent inflammatory episodes at isolated cartilaginous sites after exclusion of other possible causes and are responsive to glucocorticoids, based on the observations by other groups and our own[8, 13, 17-24] . Patients younger than 18 years or without complete electronic case files were excluded. Patients with positive anti-neutrophilic cytoplasmic antibody (ANCA) against proteinase-3 (PR3) were also excluded as suggested by Piette and colleagues [30]. The diagnosis was carefully evaluated and jointly established by a group of rheumatologists and physicians in other specialties.

Statistical Analysis

Descriptive statistics were used to describe demographic and disease characteristics, and all results were expressed as mean $\pm$ standard deviation (SD), median (range) or percentage (%) where appropriate. Continuous variables were compared using Student's t-test where the data had normal distribution or Wilcoxon rank sum test where the data were not normally distributed. Categorical variables were compared using Fisher's exact test or chi-square test, if appropriate. Correlation analysis was performed to disclose the correlation between organ involvement and correlation coefficients were calculated. A correlation coefficient $r>0$ represents positive correlation and $r<0$ represents negative correlation. Survival rates over time were plotted using the Kaplan-Meier method and compared by log rank test. A two-sided P-value <0.05 was considered to be statistically significant. Statistical analyses were performed using the SPSS version 17.0 software package (IBM).

Abbreviations

RPC: relapsing polychondritis; ANCA: anti-neutrophilic cytoplasmic antibody; CRP: C-reactive protein

Declarations

Ethics approval and consent to participate

This retrospective cohort study was approved by the Ethic Committee of Zhengzhou University (SR-2018-LW-050) and was conducted in accordance with the Declaration of Helsinki.

Consent for publication

Not applicable.

Availability of data and materials

Not applicable.

Competing interests

The authors declare no conflict of interest.

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Authors' contributions

L.Z., S.L. and T.L. designed the study; L.Z., S.Y., T.W., Y.H., J.G., L.H., J.L., X.L., R.Y. and S.Z. collected the data; L.Z. and S.Y. analyzed data, performed statistical analysis and wrote the manuscript; T.L. revised the manuscript. All authors read and approved the final manuscript.

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References

1. Lahmer T, Treiber M, von Werder A, Foerger F, Knopf A, Heemann U, et al. Relapsing polychondritis: An autoimmune disease with many faces. *Autoimmun Rev*. 2010;9:540-6. doi: 10.1016/j.autrev.2010.02.016.
2. Rednic S, Damian L, Talarico R, Scire CA, Tobias A, Costedoat-Chalumeau N, et al. Relapsing polychondritis: state of the art on clinical practice guidelines. *RMD Open*. 2018;4 Suppl 1:e000788. doi: 10.1136/rmdopen-2018-000788.
3. Kingdon J, Roscamp J, Sangle S, D'Cruz D. Relapsing polychondritis: a clinical review for rheumatologists. *Rheumatology(Oxford)*. 2018;57:1525-32. doi:10.1093/rheumatology/kex406.
4. Kent PD, Michet CJ, Jr., Luthra HS. Relapsing polychondritis. *Curr Opin Rheumatol*. 2004;16:56-61.doi:10.1097/00002281-200401000-00011
5. Hazra N, Dregan A, Charlton J, Gulliford MC, D'Cruz DP. Incidence and mortality of relapsing polychondritis in the UK: a population-based cohort study. *Rheumatology (Oxford)*. 2015;54:2181-7.doi: 10.1093/rheumatology/kev240.
6. Zhang L, Wu TG, He YJ, Guo JY, Han LS, Lu JM, et al. Diagnosing relapsing polychondritis remains a common challenge: experience from a Chinese retrospective cohort. *Clin Rheumatol* 2020. (E-pub ahead of print) doi: 10.1007/s10067-019-04852-3.
7. Lin D-F, Yang W-Q, Zhang P-P, Lv Q, Jin O, Gu J-R. Clinical and prognostic characteristics of 158 cases of relapsing polychondritis in China and review of the literature. *Rheumatology International*. 2016;36:1003-9.doi: 10.1007/s00296-016-3449-8
8. Ferrada MA, Grayson PC, Banerjee S, K AS, R AC, Sinaii N, et al. Patient Perception of Disease-Related Symptoms and Complications in Relapsing Polychondritis. *Arthritis Care Res (Hoboken)*. 2018;70:1124-31.doi: 10.1002/acr.23492.

9. Zeuner M, Straub RH, Rauh G, Albert ED, Scholmerich J, Lang B. Relapsing polychondritis: clinical and immunogenetic analysis of 62 patients. *J Rheumatol*.1997;24:96-101.
10. Belot A, Duquesne A, Job-Deslandre C, Costedoat-Chalumeau N, Boudjemaa S, Wechsler B, et al. Pediatric-onset relapsing polychondritis: case series and systematic review. *J Pediatr*. 2010;156:484-9.doi: 10.1016/j.jpeds.2009.09.045.
11. Mathew SD, Battafarano DF, Morris MJ. Relapsing polychondritis in the Department of Defense population and review of the literature. *Semin Arthritis Rheum*. 2012;42(1):70-83.doi: 10.1016/j.semarthrit.2011.12.007.
12. Sharma A, Law AD, Bamberg P, Sagar V, Wanchu A, Dhir V, et al. Relapsing polychondritis: clinical presentations, disease activity and outcomes. *Orphanet Journal of Rare Diseases*. 2014;9:198.doi: 10.1186/s13023-014-0198-1.
13. Trentham DE, Le CH. Relapsing polychondritis. *Ann Intern Med*.1998;129:114-22. doi:10.7326/0003-4819-129-2-199807150-00011
14. 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.
15. Damiani JM, Levine HL. Relapsing polychondritis—report of ten cases. *Laryngoscope*. 1979;89:929-46.
16. Michet CJ, Jr., McKenna CH, Luthra HS, O'Fallon WM. Relapsing polychondritis. Survival and predictive role of early disease manifestations. *Ann Intern Med*. 1986;104:74-8. doi:10.7326/0003-4819-104-1-74
17. Higenbottam T, Dixon J. Chondritis associated with fatal intramural bronchial fibrosis. *Thorax*. 1979;34:563-4.doi:10.1136/thx.34.4.563
18. Coppola M, Yealy DM. Relapsing polychondritis: an unusual cause of painful auricular swelling. *Ann Emerg Med*. 1992;21:81-5.doi:10.1016/s0196-0644(05)82246-2
19. Sheffield E, Corrin B. Fatal bronchial stenosis due to isolated relapsing chondritis. *Histopathology*. 1992;20:442-3. doi:10.1111/j.1365-2559.1992.tb01019.x
20. Ozbay B, Dilek FH, Yalcinkaya I, Gencer M. Relapsing polychondritis. *Respiration*. 1998;65:206-7.doi:10.1159/000029262
21. Ernst A, Rafeq S, Boisselle P, Sung A, Reddy C, Michaud G, et al. Relapsing polychondritis and airway involvement. *Chest*. 2009;135:1024-30. doi: 10.1378/chest.08-1180.
22. Maimon N, Lee P, Paul N, Hwang D, Marras TK, Keshavjee S, et al. Tracheobronchial involvement as a sole manifestation of relapsing polychondritis. *J Bronchology Interv Pulmonol*. 2010;17:5-10. doi: 10.1097/LBR.0b013e3181ca27bf.
23. Suzuki S, Ikegami A, Hirota Y, Ikusaka M. Fever and cough without pulmonary abnormalities on CT: relapsing polychondritis restricted to the airways. *Lancet*. 2015;385:88. doi: 10.1016/S0140-6736(14)61946-2.
24. Alqanatish JT, Alfarhan BA, Qubaiban SM. Limited auricular relapsing polychondritis in a child treated successfully with infliximab. *BMJ Case Rep*. 2019;12. doi: 10.1136/bcr-2018-227043.
25. Bachor E, Blevins NH, Karmody C, Kuhnel T. Otologic manifestations of relapsing polychondritis. Review of literature and report of nine cases. *Auris Nasus Larynx*. 2006;33:135-41.10.1016/j.anl.2005.11.020
26. Yang H, Peng L, Jian M, Qin L. Clinical analysis of 15 patients with relapsing auricular polychondritis. *Eur Arch Otorhinolaryngol*. 2014;271:473-6.doi: 10.1007/s00405-013-2422-3.
27. Dion J, Costedoat-Chalumeau N, Sene D, Cohen-Bittan J, Leroux G, Dion C, et al. Relapsing Polychondritis Can Be Characterized by Three Different Clinical Phenotypes: Analysis of a Recent Series of 142 Patients. *Arthritis Rheumatol*. 2016;68:2992-3001.doi: 10.1002/art.39790
28. Shimizu J, Yamano Y, Yudoh K, Suzuki N. Organ Involvement Pattern Suggests Subgroups Within Relapsing Polychondritis: Comment on the Article by Dion et al. *Arthritis & Rheumatology*. 2018;70:148-9.doi: 10.1002/art.40330.
29. Shimizu J, Yamano Y, Kawahata K, Suzuki N. Relapsing polychondritis patients were divided into three subgroups: patients with respiratory involvement (R subgroup), patients with auricular involvement (A subgroup), and overlapping patients with both involvements (O subgroup), and each group had distinctive clinical characteristics. *Medicine (Baltimore)*. 2018;97:e12837.doi: 10.1097/MD.00000000000012837.
30. Piette JC, Dion J, Costedoat-Chalumeau N. News on Relapsing Polychondritis: The Patient's Experience. *Arthritis Care Res (Hoboken)*. 2018;70:1121-3.doi: 10.1002/acr.23490.

31. Oka H, Yamano Y, Shimizu J, Yudoh K, Suzuki N. A large-scale survey of patients with relapsing polychondritis in japan. *Inflamm regen* 2014;34:149–56
32. Shimizu J, Oka H, Yamano Y, Yudoh K, Suzuki N. Cardiac involvement in relapsing polychondritis in japan[letter]. *Rheumatology (Oxford)* 2016;55:583-4. doi: 10.1093/rheumatology/kev320.
33. Kong KO, Vasoo S, Tay NS, Chng HH. Relapsing polychondritis—an Oriental case series. *Singapore Med J.* 2003;44:197-200.
34. Dion J, Costedoat-Chalumeau N, Piette J-C. Reply. *Arthritis & Rheumatology.* 2018;70:149. doi: 10.1002/art.40329.

Tables

Table 1 Characteristics of patients with relapsing polychondritis in present study and previous series.

Clinical features	Present study	Ferrada et al,2018[8]	Dion et al,2016[27]	Lin DF et al,2016 ^a [7]	Oka H et al,2014[31]	Mathew et al,2012[11]	Trentham et al,1998[13]	Zeuner et al,1997[9]	Michet et al,1986[16]	McAdam et al,1976 ^c [14]
No. of patients	126	304	142	158	239	43	66	62	112	159
Country	North China	International	France	South China	Japan	USA	USA	German	USA	USA
Study design	Retro	Survey	Retro	Retro	Survey	Retro	Retro	Survey	Retro	Retro+Liter
Demographic characteristics										
Sex, F/M	60/66	263/41	86/56	65/93	112/127	23/20	49/17	26/36	55/57	76/83
Mean age at onset, years	47.1	NA	43.5	NA	52.7	NA	NA	NA	NA	NA
Mean age at diagnosis, years	47.8	43.2	NA	45.3	NA	43	46	46.6*	51*	43.8
Follow-up, months	18(1-153)	NA	156!	NA	NA	NA	96!	11!	72(1-240)	4.3 !
Median delay, months	5(0-132)	NA#	12(0-300)	14(0.3-168)	NA	38.4**	34.8**	NA	NA	NA
Clinical features, n(%)										
Auricular chondritis	75 (59.6)	262(86.2)	127(89.4)	107(67.7)	187(78.2)	38(88.4)	62(93.9)	58(93.5)	95(84.8)	141(88.7)
Larygotracheal	60(47.7)†	NA	71(50.0)§	109(68.9)	119(49.8)‡¶	16(37.2)	44(66.7)	19(30.6)	53(47.3)	89(55.9)
Laryngeal	19(15.1)	180(59.2)	61(43.0)	45/128(35.2)†	47(19.7)	NA	NA	NA	19(16.9)	NA
Tracheobronchial	51(40.5)	225 (74.0)	32(22.5)	NA	97(40.6)	NA	NA	NA	NA	NA
Ocular inflammation	34 (26.9)	151 (49.7)	80 (56.3)	70(44.3)	109(45.6)	23(53.5)	37(56.1)	31(50.0)	57(50.9)	104(65.4)
Fever	26 (20.7)	NA	43(30.3)	NA	NA	NA	NA	15(24.2)	44(39.3)	NA
Nasal chondritis	22(17.5)	193(63.5)	89(62.7)	85(53.8)	94(39.3)	15(34.8)	32(48.5)	35(56.5)	60(53.6)	115(72.3)
Arthritis	23 (18.3)	250(82.2)	47 (33.1)	88(55.7)	92(38.5)	26(60.5)	56(84.8)	33(53.2)	58(51.8)	121(76.1)
Hearing loss	15(11.9)	104(34.2)	39(27.5)	39(24.7)	52(21.8)	16(37.2)	28(42.4)	12(19.4)	29(25.9)	65(40.9)
Costochondritis	7(5.6)	143 (47.0)	57 (40.1)	23(14.6)	NA	NA	NA	NA	NA	58(36.5)
Renal involvement	0(0)	NA	0(0)	4/134(2.5) †¶	16(6.7)	1(2.3)	NA	4(6.5)	16(14.3)	NA
Neurological involvement	6 (4.8)	NA	17 (11.9)	8/69(11.6)	23(9.6)	NA	NA	6(9.7)	NA	5(3.1)
Skin involvement	2 (1.6)	NA	40(28.2)	17/37(45.9)†	32(13.4)	NA	25(37.9)	15(24.2)	31(27.7)	26(16.4)
Valvulopathy	1(0.8)	NA	31(21.8)	3/98(3.1)†	5(2.1)^	NA	5(7.6)	0(0)	7(6.3)	14(8.8)
Arrhythmia	13(10.3)	NA	13(9.2)	1/98(1.0)†	0(0) ^	NA	NA	2(3.2)	NA	NA
MDS	1(0.8)	NA	12(8.2)	0(0)	4(1.7)	NA	NA	4(6.5)	NA	NA
Autoimmune diseases	4(3.2%)	NA	31(21.8)	17(10.8)	11(4.6)	11(25.6)	13(19.7)	22(35.5)	38(33.9)	NA

Data are presented as n(%).Retro, retrospective; Liter, literature review; NA, not available.

a A retrospective review of RP patients in one medical center in south China and cases reported in Chinese literatures.

c Among 159 patients, 23 were followed up in the author's center, the remaining 136 patients were cited from literature.

*Median age at diagnosis.

**Mean delay.

! Mean follow-up duration.

Sixty-four percent presented symptoms for more than 5 years before diagnosis.

¶ Laryngotracheal involvement was seen in 60 patients (47.7%), indicating 10 patients presented both laryngeal and tracheobronchial involvement.

Laryngotracheal involvement was seen in 71 patients (50%), indicating 22 patients presented both laryngeal and tracheobronchial involvement.

‡ Laryngotracheal involvement in 119 patients(50%) indicating 35 patients presented both laryngeal and tracheobronchial

† Denominator represents the total number in the category where datas were missing.

Mean age of 106 cases at diagnosis was 52.6 years.

^Data were extracted from another study conducted by the same authors[32].

Table 2 Classification based on organ involvement pattern*

	Organ involvement		At disease onset		During follow-up	
	Ear	Airway	Limited	Systemic	Limited	Systemic
Subgroup A	+	-	35(27.8)	29 (23.0)	25(19.8)	37(29.4)
Subgroup B	-	+	31(24.6)	18(14.3)	26(20.6)	22(17.5)
Subgroup C	+	+	0(0)	6(4.8)	0(0)	13(10.3)
Subgroup D	-	-	0(0)	7(5.6)	0(0)	3(2.4)

*Data are presented as n (%)

Table 3 Different characteristics of 4 clinical patterns.

Variables	Subgroup A	Subgroup B	Subgroup C	Subgroup D	A vs B vs C	A vs B	A vs C	B vs C
	Ear pattern	Airway pattern	Overlap pattern	A-E (-) pattern*	P value	P value	P value	P value
	(n=62)	(n=48)	(n=13)	(n=3)				
Organ involvement								
Auricular chondritis, %	100	0	100	0	<0.001	<0.001	/	<0.001
Hearing loss, %	9.7	8.3	23.1	66.7	0.293	1.000	0.183	0.159
Nasal chondritis, %	6.5	25	30.8	66.7	0.011	0.012	0.027	0.728
Ocular inflammation, %	38.7	8.3	23.1	100	0.001	<0.001	0.355	0.159
Arthritis, %	27.4	4.2	15.4	66.7	0.006	0.002	0.496	0.196
Airway involvement, %	0	100	100	0	<0.001	<0.001	<0.001	/
Tracheobronchial, %	0	89.6	61.5	0	<0.001	<0.001	<0.001	0.028
Laryngeal, %	0	27.1	46.2	0	<0.001	<0.001	<0.001	0.311
Fever, %	19.4	22.9	15.4	33.3	0.806	0.649	1.000	0.715
Costochondritis, %	3.2	10.4	0	0	0.175	0.236	1.000	0.575
Skin involvement, %	1.6	2.1	0	0	0.870	1.000	1.000	1.000
Neurological manifestation, %	6.5	2.1	0	0	0.379	0.384	1.000	1.000
Cardiac manifestation, %	12.9	8.3	7.8	0	0.696	0.546	1.000	1.000
Myelodysplasia, %	1.6	0	0	0	0.609	1.000	1.000	/
Deaths, %	1.6	29.2	23.1	0	<0.001	0.015	<0.001	1.000
Age at onset, mean $\pm$ SD, years	46.6 $\pm$ 14.4	48.2 $\pm$ 12.7	45.0 $\pm$ 15.5	46.3 $\pm$ 16.6	0.715	0.559	0.698	0.460
ESR§, median (range), mm/h	15(0-166)	53.5(0-127)	25(2-90)	53(21-95)	0.234	0.136	0.215	0.993
CRP†, median (range), mg/L	7.7(0-116.3)	36.1(0.2-165.0)	24.0(1.5-95.9)	12.7(9.9-105.0)	0.003	0.002	0.023	0.652

Note: P-values in boldface indicate statistical significance ($P < 0.05$). Airway-Ear (-) pattern was not compared with other patterns, due to limited number of patients.

* A-E (-) pattern: Airway-Ear negative pattern.

- ESR, erythrocyte sedimentation rate.

†CRP, C-reactive protein.

Figures

Figure 1

Correlation analysis of different organ involvement. The color depth is proportional to correlation strength, and red represent negative correlation while green represent positive correlation. * $P < 0.05$; ** $P < 0.01$.

Figure 2

The evolution of clinical patterns and presenting forms from disease onset to last visit.

Figure 3

Survival curve of Ear pattern, Airway pattern and Overlap pattern.