Clinical Rheumatology (2020) 39:2179–2184
https://doi.org/10.1007/s10067-019-04852-3

ORIGINAL ARTICLE

Diagnosing relapsing polychondritis remains a common challenge: experience from a Chinese retrospective cohort

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Received: 31 May 2019 / Revised: 31 October 2019 / Accepted: 11 November 2019 / Published online: 8 February 2020

Abstract

Objective The diagnosis of relapsing polychondritis (RP) is often mistaken or delayed. In this retrospective cohort, we aimed to unveil the causes responsible for such phenomenon, to determine the associated factors, and to compare diagnosis in clinical settings with the current diagnostic criteria.

Method Eighty-seven RP patients followed-up by rheumatologists from January 1, 2008, to October 31, 2018, were retrospectively analyzed.

Results A total of 50 male and 37 female patients were included with a mean age of 45.9 ± 14.5 years. Ninety-three percent were initially admitted by non-rheumatologic specialists .Twenty-eight percent were correctly diagnosed, while 72% were misdiagnosed at the first visits, all by non-rheumatologic specialists. Patients admitted by non-rheumatologic specialists had increased odds of misdiagnosis (odds ratio [OR] = 1.3, 95% confidence interval [95% CI] 1.1–1.7, $P = 0.000$). Fifty-seven (65.5%) patients did not meet with Michet or Damiani criteria, with 16 (18.4%) patients diagnosed as partial RP and 41(47.1%) patients diagnosed as limited RP.

Conclusions Incorrect and delayed diagnosis of RP is common in our cohort, and insufficient awareness of the disease in non-rheumatologic specialists at least partially contributes to this. It is imperative to revise the current criteria for early diagnosis.

Key Points

- *Diagnosing relapsing polychondritis (RP) in early stage remains challenging after all these years, especially among non-rheumatologic specialists, indicating the importance of teaching non-rheumatologic specialists to improve their understanding of this rare disease.*
- *Many RP patients did not fully meet with the current criteria, suggesting that revision of the current criteria is imperative for early diagnosis of this rare disease.*

Keywords Clinical features · Criteria · Delay · Misdiagnosis · Relapsing polychondritis

Introduction

Relapsing polychondritis (RP) is a rare autoimmune disease of unknown etiology, and its typical clinical manifestation is recurrent and progressive inflammation of the cartilaginous tissue in various sites of the body [1–3]. An Austria physician Jaksch-Wartenhorst firstly described the syndrome of fever, polyarthritis, and deformities of ear and nose as "polychondropathia." The current name of RP was firstly used by Pearson and colleagues in 1960 [4]. The incidence of RP was about 3.5 per million per year in the USA [5] and 0.71 per million population per year between 1990 and 2012 in the UK [6]. However, epidemiologic data of RP is not currently available in China. Several case series of different sizes were previously reported with the majority of the patients being Caucasians [6–15], and information about East Asians is scarce [16–20].

RP predominantly affects cartilaginous tissue, causing destruction of the ears, nose, and trachea. Of note, lesions may also occur in extra-cartilaginous tissues including the eyes, heart, skin, and central nervous and hematological systems (myelodysplastic syndrome [MDS] is the most frequent). Patients may visit physicians at different departments due to

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protean manifestations of RP, and common departments include otolaryngology, pulmonology, ophthalmology, primary care, dermatology, etc. [3, 7, 19]. Patients often experience a misdiagnosis [19] or a significant delay in the diagnosis [10, 12–14, 18, 19]. However, the associated factors have not been extensively studied before. Therefore, our current study aimed to share our experience in diagnosing RP from patients in central China and to determine the factors associated with incorrect or delayed diagnoses.

Materials and methods

Patient selection

RP patients that were hospitalized and followed up by rheumatologists at our hospital between January 1, 2008, and October 31, 2018, were included for retrospective analysis. RP was defined according to the criteria proposed by Michet [7] and Damiani et al. [9]. Partial RP was also designated if patients undergo recurrent chondritis associated with deformity, accompanied with vestibular dysfunction, ocular inflammation, or inflammatory arthritis as suggested by Mathew et al. [14]. RP can also be diagnosed if patients presented with recurrent inflammatory episodes at isolated cartilaginous sites after ruling out any other possible causes and are responsive to glucocorticoids, namely, limited RP, according to previous reports [11, 21–23] and our own experience. 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 [24]. The diagnosis was reevaluated and jointly made by a group of specialists in the relevant fields.

Demographic data, initial diagnosis, the department of the first visit and manifestations at the first visit, and the time when final diagnosis was established and thereafter before the last follow-up were recorded. The last follow-up was defined as the most recent visit, the time when the patient died or the time we called back. The recorded clinical data included manifestations associated with external ear, nose, larynx, joints, costochondral cartilage, tracheobronchial tree, audiovestibular system, eye, heart, skin, and central nervous system involvement, as well as constitutional symptoms.

This retrospective study was approved by the Ethic Committee of Zhengzhou University (SR-2018-LW-050) and was conducted in accordance with the Declaration of Helsinki. When analyzing the data, personal information, such as name and hospital number, were replaced by index numbers.

Statistical analysis

Descriptive statistics were used to describe demographic and disease characteristics, and all results were expressed as mean ± standard deviation (SD) , median (range), or percentage (%) where appropriate. Comparisons of continuous variables were performed using Student's t-test where the data have normal distribution or Wilcoxon rank sum test where the data were not normally distributed. Categorical data were compared using chi-squared or Fisher's exact test. Kaplan–Meier curves were generated to estimate the survival rates. Statistical significance was defined as two-sided P value < 0.05. Statistical analyses were performed using the SPSS version 17.0 software package (IBM).

Results

Patients' profiles

A total of 50 male and 37 female patients were included with a mean age of 45.9 ± 14.5 years at presentation and were followed up after the establishment of diagnosis for a median of 25 months (4–124 months), with 31 patients followed up for at least 36 months, 45 patients for at least 24 months, and 71 patients for at least 12 months (Table 1).

At presentation, only 6 patients (6.9%) were admitted by rheumatologists , whereas 81 patients (93.1%) were admitted by non-rheumatologic specialists, including 38 patients by ear, nose, and throat (ENT) specialists, 25 by pulmonologists, and the rest 18 by other specialists (detailed in Fig. 1). All patients presented to pulmonologists reported symptoms associated with laryngotracheal involvement as the main problem, and 94.7% of patients presented to ENT specialists reported auricular chondritis as the main problem (5.3% reported hoarseness as the main problem), indicating that the first visited specialists were closely associated with the organ initially involved .

Clinical features

The most frequent initial features included auricular chondritis (57.5%) and laryngotracheal involvement (42.5%), followed by ocular inflammation (24.1%), fever (18.4%), nasal chondritis (16.1%), arthritis (14.9%), hearing loss (9.2%), costochondritis (2.3%), neurological involvement (1.1%), dermatological manifestations (1.1%), arrhythmia (1.1%), and MDS (1.1%). More features developed at the time of diagnosis and during follow-up, which were detailed in Fig. 2. Much attention should be paid to that some features remained stable during follow-up, indicating no disease progression in some patients.

Table 1 Demographic characteristics of RP patients

	All patients (n = 87)	Correctly-diagnosed patients(n = 24)	Misdiagnosed patients(n = 63)	*P* *
Age at disease onset, mean ± SD years	45.9 ± 14.5	41.8 ± 15.2	47.6 ± 14.1	0.101†
Female, no. (%)	37 (42.5)	6 (25.0)	31 (49.2)	0.041‡
Follow-up, median (range) months	25 (4–124)	31 (5–87)	20 (4–124)	0.827§
Disease duration at diagnosis, median (range) months	5 (0.4–71)	2 (0.4–12)	7 (1–71)	0.000§
Deaths, no. (%)	12 (13.8)	0 (0)	12 (19.0)	0.032¶

*Compared between correctly diagnosed patients and misdiagnosed patients

†Student's t-test , t = −1.659

‡Chi-squared test.χ^2 = 4.166

§Wilcoxon rank sum test

¶Fisher's exact test

Misdiagnosis at first visit

Twenty-four patients (27.6%) were correctly diagnosed at their first visits, 6 by rheumatologists, and 18 by non-rheumatologic specialists (mainly pulmonologists and ENT specialists). However, 63 patients (72.4%) were misdiagnosed at their first visits, all by non-rheumatologic specialists, including 19 cases by pulmonologists, 28 cases by ENT specialists, and the rest 16 cases by other specialists. Patients admitted by non-rheumatologic specialists had increased odds for misdiagnosis (OR = 1.3, 95% CI 1.1–1.7, *P* = 0.000). Correct diagnosis of misdiagnosed patients was finally made by rheumatologists in 46 cases (73.0%) and by non-rheumatologic specialists in 17 cases (27.0%). There was a median diagnostic delay of 6 months (range: 0.5–71 months), of which 15 patients were delayed for over a year. The demographic data were comparable between misdiagnosed and correctly diagnosed patients except that misdiagnosed patients had a significant female dominance (49.2% vs 25.0%, *P* = 0.041) and more deaths than correctly diagnosed patients (19% vs 0%, *P* = 0.032) (Table 1).

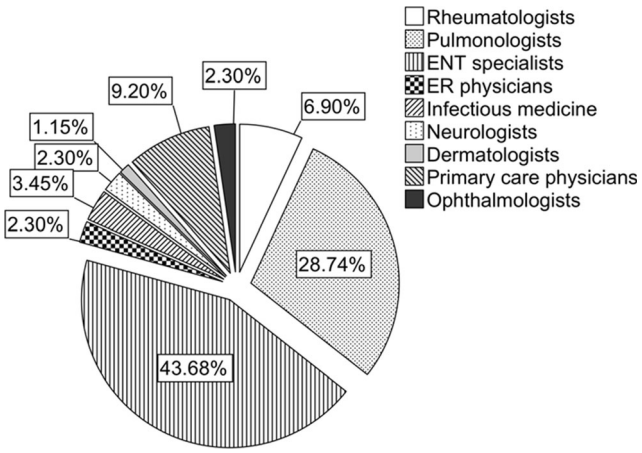

Fig. 1 Percentages of subspecialties admitted to at initial presentation. ENT,Ear,Nose & Throat. ER,emergency room

The initial diagnoses of 19 patients misdiagnosed by pulmonologists included bacterial pneumonia (9 cases), amyloidosis of the trachea (5 cases), asthma (3 case), fever of unknown origin (1 case), and pharyngitis (1 case). It was noteworthy that lung computed tomography (CT) scan of 16 patients revealed typical features of RP; however, 10 of them were neglected by both radiologists and pulmonologists.

The initial diagnoses of 28 patients misdiagnosed by ENT specialists included perichondritis (13 cases), auricular pseudocyst (5 cases), auricle infection (8 cases), and laryngitis (2 cases). Of note, five patients were treated with the resection of the auricles. Only 4 out of 28 patients received lung CT scan, indicating a general unawareness of this rare systemic disease.

The initial diagnoses of the remaining 16 patients included fever of unknown origin (6 cases), pneumonia(2 cases), bronchiectasis (1 case), autoimmune encephalitis (1 case), auricle infection (1 case), otitis media (1 case), uveitis (2 cases), conjunctivitis (1 case), and rheumatoid arthritis (1 case).

Survivals

There were 12 deaths (13.8%) of our patients, and the main causes of deaths included refractory disease in 8 patients (66.7%), pulmonary infection in 3 patients (25%), and unknown in 1 patient (8.3%). All 12 deaths of our patients had laryngotracheal involvement and were misdiagnosed initially, 11 by pulmonologists and 1 by ENT specialists. The probability of survival was statistically different between patients with and without laryngotracheal involvement and between misdiagnosed and correctly diagnosed patients (Fig. 3).

Matching with current criteria

Fifty-seven (65.5%) patients did not meet with Michet or Damiani criteria, with 16 (18.4%) patients diagnosed as partial RP and 41(47.1%) patients diagnosed as limited RP, among

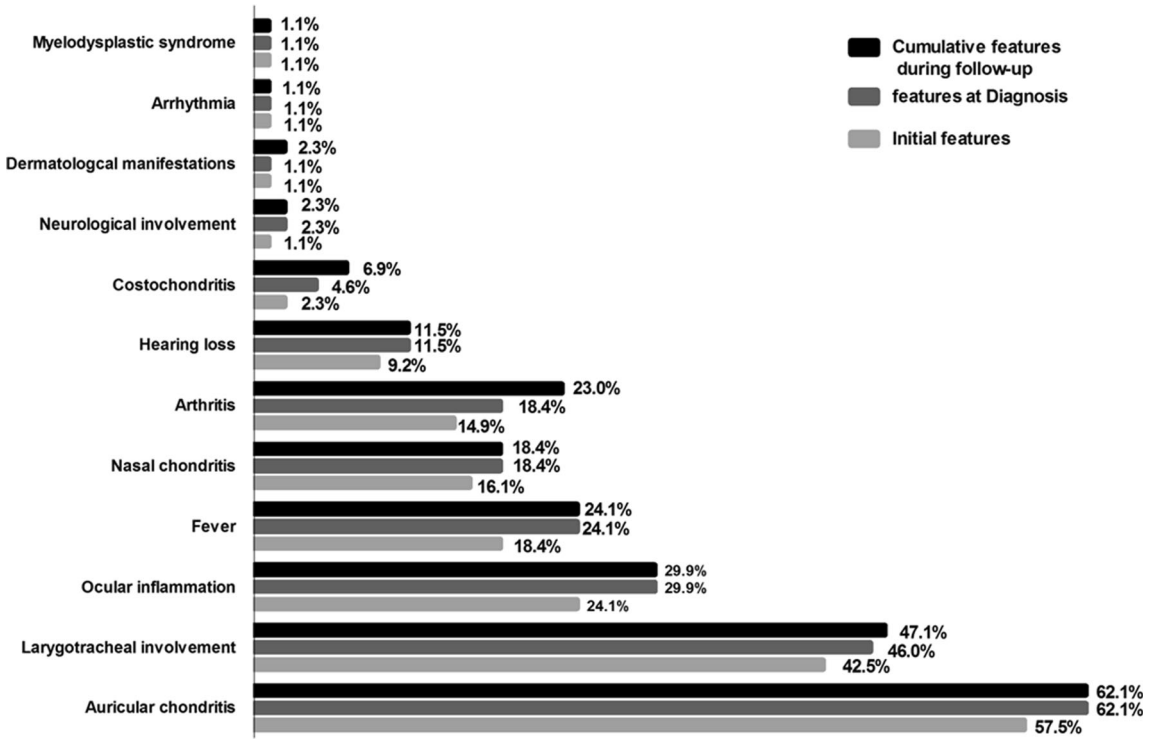

Fig. 2 Clinical features at presentation ,diagnosis and during follow-up

which 20 presented with laryngotracheal involvement and 21 with auricular chondritis as the main or sole manifestation. During follow-up, two limited RP patients developed arthritis and met partial RP criteria, while one limited RP patient developed laryngotracheal lesion and met the Michet or the Damiani criteria. Two partial RP patients developed arthritis and met the Michet or Damiani criteria.

Discussion

Our retrospective study has demonstrated that incorrect and delayed diagnosis is common in clinical practice, and insufficient awareness of the disease in non-rheumatologic specialists at least partially contributes to this. Delayed diagnosis leads to delayed treatment and disastrous consequences in laryngotracheal involved patients. Moreover, many of our patients did not fully meet with the previously established criteria, suggesting that the revision of these criteria is imperative for early diagnosis.

The age at diagnosis of our patients was comparable to previous reports. The diagnostic delay was much shorter than the previous study (1–2.9 years) [10, 12–14, 18, 19], demonstrating that more RP patients in early stage were included in our study. Compared to the observations made by Lin and colleagues in Southern China [19], our results showed a slight male predominance. A higher frequency of auricular chondritis and ocular inflammation but slightly lower incidences of arthritis, nasal chondritis, and skin and neurological involvement were also noted as compared to their study [19]. The discrepancy may be due to different population selections. In concordance with Lin's findings [19], the patients in our study had a higher initial frequency of laryngotracheal involvement than the Caucasians (14%–38% initially), demonstrating more severe disease in Chinese population, consistent with the observations made by Kong et al. [16]. However, the cumulative features increased during follow-up with a comparable frequency of laryngotracheal involvement to Caucasians (30%–67%) but with a lower cumulative frequency of other features, which may be due to the shorter follow-up period of our study.

RP patients were easily admitted by non-rheumatologic specialists, especially ENT specialists and pulmonologists [6, 19]. Most misdiagnosis and diagnostic delay occurred at ENT and pulmonology department and were associated more deaths especially among laryngotracheal involved patients indicating an important role of ENT specialists and pulmonologists for early recognition of this rare disease to avoid deaths [25–27]. We suggest timely communication between non-rheumatologic specialists and rheumatologists.

Most misdiagnosed patients were eventually recognized by rheumatologists, suggesting the role of rheumatologists in establishing the diagnosis. The neglect of typical CT features by pulmonologists and lower rate of performing chest CT scan in patients admitted to ENT specialists indicate an insufficient awareness of and a lack of vigilance to the disease among

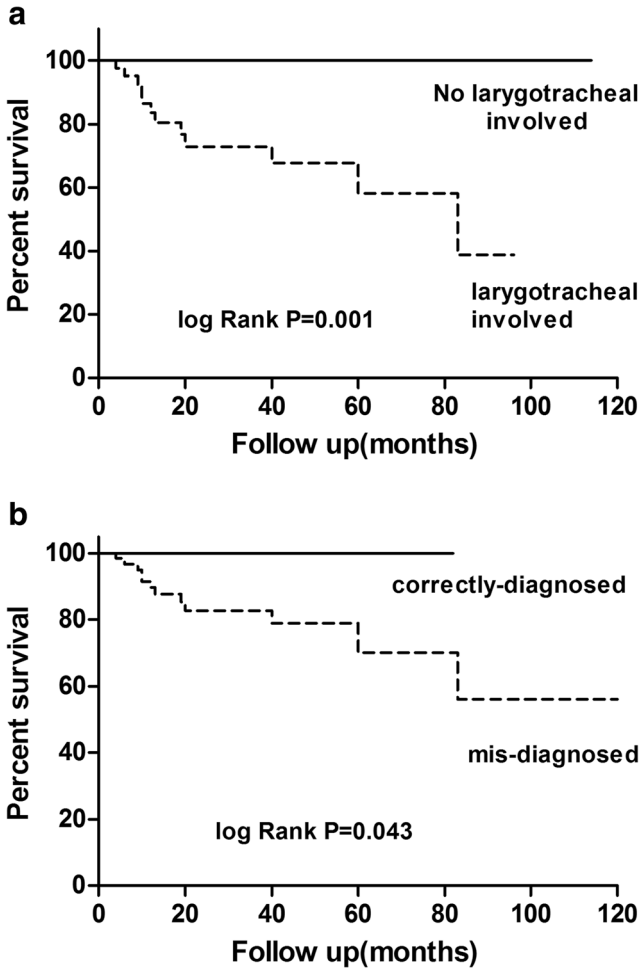

Fig. 3 Kaplan-Meier analysis of the probability of survival. The log rank test was used to compare survival probabilities. A. Survival curve between patients with and without laryngotracheal involvement. B. Survival curve between misdiagnosed patients and correctly diagnosed patients

non-rheumatologic specialists. Bachor et al. [26] and Yang et al. [27] have provided some useful approaches to avoid misdiagnosis.

Overall, 57 of our patients did not meet with traditional criteria suggested by Michet et al. [7] and Damiani et al. [9], with 16 diagnosed as partial RP and the remaining 41 patients diagnosed as limited RP. During follow-up periods, only three patients progressed to meet with the traditional criteria. This may indicate that RP patients not meeting with traditional criteria are quite common in clinical practice. Patients with laryngotracheal manifestation or auricular inflammation as the only initial feature of the disease [11, 21] or even as the sole feature [22, 23] have been reported. However, limited RP has not been reported in relatively large case series. We believe that this is the first time to elucidate this issue in case series. It should be noticed that laryngotracheal involvement is a predictor for poor outcome, and delays in the diagnosis might result in disastrous consequences. However, the criteria suggested by Michet et al. [7] and Damiani et al. [9] easily miss this part of patients in the early stage of presentation [14]. Thus, new criteria or scoring system incorporating biomarkers and imaging studies is expected to facilitate prompt diagnosis.

There are some limitations of our study. First, the retrospective nature may induce some bias. Second, the inclusion of only hospitalized patients can miss some out-clinic patients causing incomplete inclusion of clinical features. Third, the study size was relatively small, and only a minor portion of patients visited rheumatologists for the first time, which might overestimate the misdiagnosis rate.

In conclusion, incorrect and delayed diagnoses are common in RP, at least partially due to the initial insufficient manifestations and insufficient awareness of the disease among non-rheumatologic specialists. Thus, it is imperative to teach non-rheumatologic specialists and especially pulmonologists and ENT specialists to decrease the incidences of a misdiagnosis and delays in diagnosing the disease. And updating the criteria is another way to improve the diagnosis of this rare disease.

Funding information The authors received no financial and material support.

Data availability Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

Compliance with ethical standards

Disclosures None.

Ethical approval This retrospective study was approved by the Ethic Committee of Zhengzhou University (SR-2018-LW-050) and was conducted in accordance with the Declaration of Helsinki. When analyzing the data, personal information such as name, hospital number, etc. were replaced by index numbers.

References

1. Lahmer T, Treiber M, von Werder A, Foerger F, Knopf A, Heemann U, Thuermel K (2010) Relapsing polychondritis: an autoimmune disease with many faces. Autoimmun Rev 9(8):540–546. https://doi.org/10.1016/j.autrev.2010.02.016
2. Cantarini L, Vitale A, Brizi MG, Caso F, Frediani B, Punzi L, Galeazzi M, Rigante D (2014) Diagnosis and classification of relapsing polychondritis. J Autoimmun 48-49:53–59. https://doi.org/10.1016/j.jaut.2014.01.026
3. Longo L, Greco A, Rea A, Lo Vasco VR, De Virgilio A, De Vincentiis M (2016) Relapsing polychondritis: a clinical update. Autoimmun Rev 15(6):539–543. https://doi.org/10.1016/j.autrev.2016.02.013
4. Pearson CM, Kline HM, Newcomer VD (1960) Relapsing polychondritis. N Engl J Med 263:51–58. https://doi.org/10.1056/NEJM196007142630201
5. Kent PD, Michet CJJ, Luthra HS (2004) Relapsing polychondritis. CurrOpinRheumatol 16:56–61

6. Hazra N, Dregan A, Charlton J, Gulliford MC, D'Cruz DP (2015) Incidence and mortality of relapsing polychondritis in the UK: a population-based cohort study. Rheumatology (Oxford) 54(12): 2181–2187. https://doi.org/10.1093/rheumatology/kev240
7. Michet CJ Jr, McKenna CH, Luthra HS, O'Fallon WM (1986) Relapsing polychondritis. Survival and predictive role of early disease manifestations. Ann Intern Med 104(1):74–78
8. McAdam LP, O'Hanlan MA, Bluestone R, Pearson CM (1976) Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore) 55(3):193–215
9. Damiani JM, Levine HL (1979) Relapsing polychondritis–report of ten cases. Laryngoscope 89(6 Pt 1):929–946
10. Zeuner M, Straub RH, Rauh G, Albert ED, Scholmerich J, Lang B (1997) Relapsing polychondritis: clinical and immunogenetic analysis of 62 patients. J Rheumatol 24(1):96–101
11. Trentham DE, Le CH (1998) Relapsing polychondritis. Ann Intern Med 129(2):114–122
12. Frances C, el Rassi R, Laporte JL, Rybojad M, Papo T, Piette JC (2001) Dermatologic manifestations of relapsing polychondritis. A study of 200 cases at a single center. Medicine (Baltimore) 80(3): 173–179
13. Belot A, Duquesne A, Job-Deslandre C, Costedoat-Chalumeau N, Boudjemaa S, Wechsler B, Cochat P, Piette JC, Cimaz R (2010) Pediatric-onset relapsing polychondritis: case series and systematic review. J Pediatr 156(3):484–489. https://doi.org/10.1016/j.jpeds.2009.09.045
14. Mathew SD, Battafarano DF, Morris MJ (2012) Relapsing polychondritis in the Department of Defense population and review of the literature. Semin Arthritis Rheum 42(1):70–83. https://doi.org/10.1016/j.semarthrit.2011.12.007
15. Dion J, Costedoat-Chalumeau N, Sene D, Cohen-Bittan J, Leroux G, Dion C, Frances C, Piette JC (2016) Relapsing polychondritis can be characterized by three different clinical phenotypes: analysis of a recent series of 142 patients. Arthritis Rheum 68(12):2992–3001. https://doi.org/10.1002/art.39790
16. Kong KO, Vasoo S, Tay NS, Chng HH (2003) Relapsing polychondritis–an oriental case series. Singap Med J 44(4):197–200
17. Oka H, Yamano Y, Shimizu J, Yudoh K, Suzuki N (2014) A large-scale survey of patients with relapsing polychondritis in Japan. Inflamm Regen 34:149–156
18. Sharma A, Law AD, Bambery P, Sagar V, Wanchu A, Dhir V, Vijayvergiya R, Sharma K, Gupta A, Panda NK, Singh S (2014) Relapsing polychondritis: clinical presentations, disease activity and outcomes. Orphanet J Rare Dis 9:198. https://doi.org/10.1186/s13023-014-0198-1
19. Lin DF, Yang WQ, Zhang PP, Lv Q, Jin O, Gu JR (2016) Clinical and prognostic characteristics of 158 cases of relapsing polychondritis in China and review of the literature. Rheumatol Int 36(7):1003–1009. https://doi.org/10.1007/s00296-016-3449-8
20. Chuah TY, Lui NL (2017) Relapsing polychondritis in Singapore: a case series and review of literature. Singapore Med J 58(4):201–205. https://doi.org/10.11622/smedj.2016047
21. Ernst A, Rafeq S, Boiselle P, Sung A, Reddy C, Michaud G, Majid A, Herth FJF, Trentham D (2009) Relapsing polychondritis and airway involvement. Chest 135(4):1024–1030. https://doi.org/10.1378/chest.08-1180
22. Maimon N, Lee P, Paul N, Hwang D, Marras TK, Keshavjee S, Chan CK (2010) Tracheobronchial involvement as a sole manifestation of relapsing polychondritis. J Bronchology Interv Pulmonol 17(1):5–10. https://doi.org/10.1097/LBR.0b013e3181ca27bf
23. Ozbay B, Dilek FH, Yalcinkaya I, Gencer M (1998) Relapsing polychondritis. Respiration 65(3):206–207. https://doi.org/10.1159/000029262
24. Piette JC, Dion J, Costedoat-Chalumeau N (2018) News on relapsing polychondritis: the patient's experience. Arthritis Care Res 70(8):1121–1123. https://doi.org/10.1002/acr.23490
25. Vitale A, Sota J, Rigante D, Lopalco G, Molinaro F, Messina M, Iannone F, Cantarini L (2016) Relapsing polychondritis: an update on pathogenesis, clinical features, diagnostic tools, and therapeutic perspectives. Curr Rheumatol Rep 18(1):3. https://doi.org/10.1007/s11926-015-0549-5
26. Bachor E, Blevins NH, Karmody C, Kuhnel T (2006) Otologic manifestations of relapsing polychondritis. Review of literature and report of nine cases. Auris Nasus Larynx 33(2):135–141. https://doi.org/10.1016/j.anl.2005.11.020
27. Yang H, Peng L, Jian M, Qin L (2014) Clinical analysis of 15 patients with relapsing auricular polychondritis. Eur Arch Otorhinolaryngol 271(3):473–476. https://doi.org/10.1007/s00405-013-2422-3