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BRIEF REPORT

Defining Clinical Subgroups in Relapsing Polychondritis: A Prospective Observational Cohort Study

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Objective. Relapsing polychondritis (RP) is a systemic disease. Failure to recognize RP can lead to diagnostic delay and further complications, including death. This study was undertaken to identify clinical patterns in a prospective cohort of patients with RP.

Methods. Patient subgroups were identified using latent class analysis based on 8 clinical variables: saddle-nose deformity, subglottic stenosis, tracheomalacia, bronchomalacia, ear chondritis, tenosynovitis/synovitis, inflammatory eye disease, and audiovestibular disease. Model selection was based on Akaike's information criterion.

Results. Seventy-three patients were included in this study. Patients were classified into 1 of 3 subgroups: type 1 RP (14%), type 2 RP (29%), and type 3 RP (58%). Type 1 RP was characterized by ear chondritis (100%), tracheomalacia (100%), saddle-nose deformity (90%), and subglottic stenosis (80%). These patients had the shortest median time to diagnosis (1 year), highest disease activity, and greatest frequency of admission to the intensive care unit and tracheostomy. Type 2 RP was characterized by tracheomalacia (100%) and bronchomalacia (52%), but no saddle-nose deformity or subglottic stenosis. These patients had the longest median time to diagnosis (10 years) and highest percentage of work disability. Type 3 RP was characterized by tenosynovitis/synovitis (60%) and ear chondritis (55%). There were no significant differences in sex, race, or treatment strategies between the 3 subgroups.

Conclusion. Our findings indicate that there are 3 subgroups of patients with RP, with differences in time to diagnosis, clinical and radiologic characteristics, and disease-related complications. Recognizing a broader spectrum of clinical patterns in RP, beyond cartilaginous involvement of the ear and upper airway, may facilitate more timely diagnosis.

INTRODUCTION

Relapsing polychondritis (RP) is a rare, systemic, and in some cases, fatal inflammatory disease with a predilection for cartilaginous structures (1,2). Although auricular chondritis is often considered the hallmark feature of the disease, RP can affect multiple organs, including the tracheobronchial tree, upper airway, nose, joints, central nervous system, eyes, inner ear, blood vessels, heart valves, and skin. Due to potential widespread organ involvement, clinical manifestations may vary, and recognizing the disease across a range of presentations can be challenging.

Early identification of RP, with prompt initiation of treatment, may help decrease uncontrolled inflammation and ultimate organ damage. RP carries significant morbidity, including tracheomalacia, subglottic stenosis, intensive care unit (ICU) admissions, hearing loss, and disability (3,4). Significant mortality is also associated with RP, with an incidence rate ranging from 55% to 91% 10 years after diagnosis (3,5). Diagnostic delay is common, with reported time to diagnosis ranging anywhere from 1 year to 20 years (4,6). Lack of auricular chondritis has been associated with diagnostic delay, indicating that broader understanding of the spectrum of possible clinical manifestations and patterns of organ involvement could facilitate a more timely diagnosis (4).

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Defining disease subgroups in RP based on clinical and radiographic features may enable earlier diagnoses, while also leading to the development of diagnostic and treatment algorithms. Therefore, the objective of the present study was to employ unbiased analytical approaches to identify subgroups of patients with RP based on clinical patterns of disease.

PATIENTS AND METHODS

Study population. Patients age ≥18 years were recruited into a prospective observational RP cohort regarding RP at the National Institutes of Health (NIH). All patients met the McAdams or Damiani diagnostic criteria for RP (7,8). Patients could be enrolled at any point in their disease course. All patients provided written informed consent, and the study protocol was approved by local ethics review (approval no. 14-AR-0200).

Clinical assessments and disease definitions. All patients had a consultation at the NIH Clinical Center. A detailed, standardized clinical assessment was performed by the investigative study team. Findings attributed to RP were recorded using standardized case report forms. All patients underwent audiology testing and standardized assessment of the airways, including a dynamic computed tomography (CT) scan of the chest, direct laryngoscopy by an otolaryngologist, and pulmonary function tests (PFTs). Outside clinical records were directly reviewed by the study team. Bronchoscopy was not performed as part of standardized assessment; however, data from prior bronchoscopies were recorded. Every patient underwent clinical laboratory testing, which included erythrocyte sedimentation rate, C-reactive protein level, complete blood cell count, comprehensive metabolic panel, lipid panel, testing for antineutrophil cytoplasmic antibodies (ANCAs), lupus anticoagulant, anticardiolipin antibodies, rheumatoid factor, antinuclear antibodies, anti–double-stranded DNA antibodies, extractable nuclear antigens, and urinalysis.

Standardized definitions were applied to disease-relevant features. Ear chondritis was defined as physician-observed tender swelling of the pinna with associated redness; and/or cauliflower ear; and/or other evidence of cartilage damage, including floppy ears and/or thickened cartilage. Sinonasal disease was defined as tenderness over the bridge of the nose with redness and/or swelling, tenderness of the tip of the nose with associated swelling and/or redness, saddle-nose deformity, nasal crusting, or nasal septal perforation. Airway chondritis was defined as tracheomalacia, bronchomalacia, tracheal thickening, or subglottic stenosis. Tracheomalacia was defined as anterior and/or lateral flattening of the tracheal wall of ≥50%, visualized during bronchoscopy or dynamic CT scan (9). Bronchomalacia was defined as bronchial collapse, visualized during bronchoscopy or dynamic CT scan. Tracheal thickening was defined as >3 mm wall thickness as measured by chest CT (10). Subglottic stenosis was defined as pathologic narrowing of the subglottis visualized by direct laryngoscopy. Arthritis was defined as physician-observed synovitis/tenosynovitis. Vestibular/cochlear damage was defined as documented sensorineural hearing loss on audiometry and/or documented vestibular dysfunction on vestibular testing. Ocular inflammation was defined as physician-observed scleritis, episcleritis, iritis, or uveitis. Skin involvement was defined as a biopsy-proven skin pathology clinically attributed to RP. Disease activity is defined by the physician global assessment score, rated on a scale of 0–10, with higher scores indicating higher disease activity. A physician global assessment score >0 indicated active disease.

Statistical analysis. Latent class analysis was performed to identify subsets of patients with RP based on predefined input variables. Latent class analysis is an unbiased partitioning method that can be used to classify individuals into subgroups that share similar characteristics based on a set of categorical input variables. Input variables for latent class analysis modeling were chosen a priori based on criterion items from the McAdams diagnostic criteria for RP. Variables that represented objective cartilaginous involvement were selected, including ear chondritis, saddle-nose deformity as a surrogate for nose chondritis, airway chondritis (subglottic stenosis, tracheomalacia, bronchomalacia), arthritis/tenosynovitis, sensorineural hearing loss or vestibular dysfunction, and inflammatory eye disease. Airway chondritis was divided into 3 different anatomic locations to differentiate upper airway involvement from lower airway involvement, since patients with RP can have isolated upper or lower airway disease.

Model fit was assessed using Akaike's information criterion (AIC). Models were fit with 2–6 subgroups, and the model with the lowest AIC was ultimately selected (Supplementary Table 1, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41270/abstract). Each resultant subgroup was labeled with a descriptive term based on the common manifestations defining the group. Categorical and continuous variables were compared using the chi-square test or Kruskal-Wallis test. Data are presented as the median (interquartile range [IQR]). All analyses were performed using JMP version 14. *P* values less than 0.05 were considered significant, and adjustment for repeated measures was not performed given the exploratory nature of the study and modest sample size.

RESULTS

Clinical characteristics of the study participants. A total of 73 patients were included in the analyses. Most patients were female (n = 62 [85%]) and white (n = 63 [86%]). The median age at symptom onset was 36 years (IQR 28–43 years) and the median age at diagnosis was 43 years (IQR 33–59 years). The median time to diagnosis was 5 years (IQR 2–10 years). The median disease duration was 8 years (IQR 4–15 years).

Severe organ damage was not uncommon, including saddle-nose deformity (n = 10 [14%]), subglottic stenosis (n = 11 [15%]),

tracheomalacia (n = 31 [42%]), bronchomalacia (n = 16 [22%]), and hearing loss (n = 19 [26%]). Four patients (5%) had nasal septal perforation, 2 patients (3%) had scleromalacia, 1 patient (1%) had vestibular dysfunction, and 1 patient (1%) had severe aortic insufficiency. Other significant disease-related complications included work disability (n = 25 [34%]) and ICU admission due to RP (n = 12 [16%]). Most patients were taking disease-modifying antirheumatic drugs (DMARDs) at the time of initial evaluation (n = 49 [67%]). Most patients received prednisone ≥60 mg per day (n = 36 [50%]) at some point in the disease course as part of their treatment. Every patient had active disease at the baseline visit. No patient was positive for anti–proteinase 3 ANCA or anti-myeloperoxidase ANCA.

Analytical identification of subgroups. Latent class analysis identified 3 subgroups of patients with RP based on clinical manifestations. The first subgroup (n = 10 [14%]) was characterized by ear chondritis (100%), tracheomalacia (100%), saddle-nose deformity (90%), subglottic stenosis (80%), tenosynovitis/synovitis (60%), bronchomalacia (50%), hearing loss (50%), and inflammatory eye disease (40%). This group, defined by extensive cartilage damage and ear involvement, was labeled type 1 RP. The second subgroup (n = 21 [29%]) was characterized by tracheomalacia (100%), bronchomalacia (52%), tenosynovitis/synovitis (52%), ear chondritis (43%), hearing loss (33%), and inflammatory eye disease (19%), in the absence of saddle-nose deformity and subglottic stenosis (Supplementary Table 2, available on the *Arthritis & Rheumatology* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.41270/abstract). This group, characterized by prominent lower airway disease with less overt involvement of cranial cartilaginous structures, was labeled type 2 RP. The final subgroup (n = 42, 58%) was characterized by tenosynovitis/synovitis (60%), ear chondritis (55%), inflammatory eye disease (26%), and hearing loss (19%). This group, defined by minimal overt cartilage damage including subglottic stenosis (7%), and saddle-nose deformity (2%) without evidence of tracheomalacia or bronchomalacia, was labeled type 3 RP (Figure 1).

When the 3 subgroups were compared, there were no differences in demographic characteristics, including race, sex, age at symptom onset, age at diagnosis, and disease duration. Two patients, 1 in the type 1 RP subgroup and 1 in the type 2 RP subgroup, died, and the cause of death was not directly related to RP. Compared to the other subgroups, patients with type 1 RP experienced the shortest time to diagnosis (median 1 year [IQR 0.6–5 years]; $P = 0.007$), were the youngest at the time of diagnosis (median age 39 years [IQR 23–49 years]; $P = 0.08$), and had the highest disease activity (median physician global assessment score 5 [IQR 3.75–6]). Patients with type 2 RP experienced the longest time to diagnosis (median 10 years [IQR 3.5–20 years]; $P = 0.007$) and were the oldest at the time of diagnosis (median age 48 years [IQR 43–56 years]; $P = 0.08$) (Table 1).

The prevalence of additional symptoms not included as input variables in the latent class analysis models was compared among the subgroups. Patients with type 1 RP reported a significantly greater prevalence of weight loss (40% versus 0% in the type 2 RP subgroup and 9% in the type 3 RP subgroup; $P = 0.02$), and stridor (70% versus 0% in the type 2 RP subgroup and 7% in the type 3 RP subgroup; $P < 0.0001$). Patients with type 2

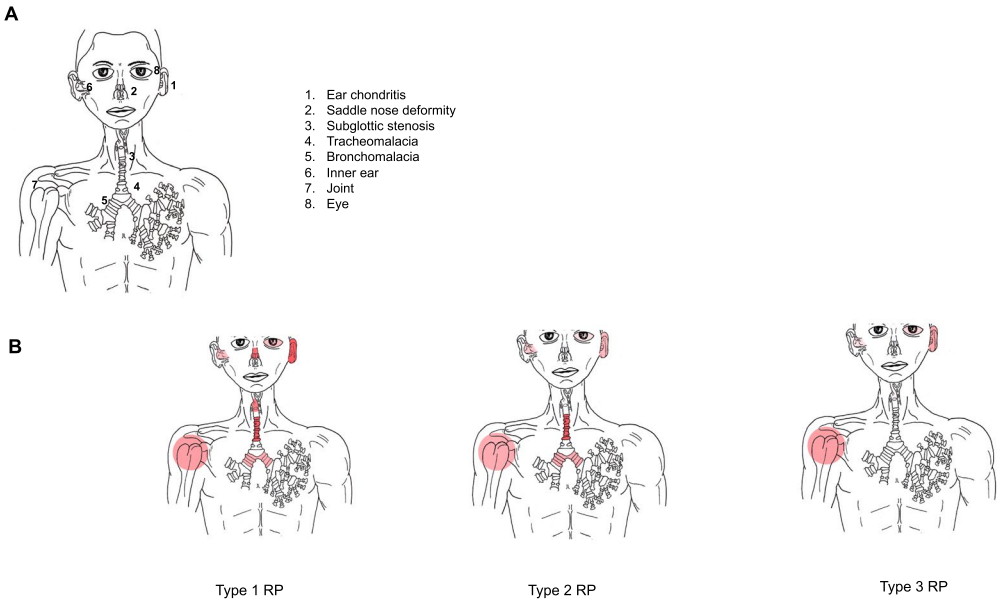

Figure 1. Characteristics and subtypes of relapsing polychondritis (RP). **A**,Variables used in latent class analysis modeling. Variables were chosen based on criterion items from the McAdams diagnostic criteria for RP. **B**, Illustrations representing the 3 clinical subtypes of RP identified by latent class analysis. Shading indicates the percentage of organ involvement for type 1 RP, type 2 RP, and type 3 RP. Darker shading indicates a higher percentage of involvement.

Table 1. Clinical characteristics of 3 subgroups of patients with RP*

	All patients (n = 73)	Type 1 RP (n = 10)	Type 2 RP (n = 21)	Type 3 RP (n = 42)	*P*
Variables included in latent class analysis					
Saddle-nose deformity	10 (13)	9 (90)	0 (0)	1 (2)	<0.001
Subglottic stenosis	11 (15)	8 (80)	0 (0)	3 (7)	<0.001
Tracheomalacia	31 (42)	10 (100)	21 (100)	0 (0)	<0.001
Bronchomalacia	16 (22)	5 (50)	11 (52)	0 (0)	<0.001
Ear chondritis	42 (57)	10 (100)	9 (43)	23 (55)	0.001
Tenosynovitis/synovitis	42 (57)	6 (60)	11 (52)	25 (60)	0.85
Inflammatory eye disease	20 (27)	4 (40)	4 (19)	11 (26)	0.47
Sensorineural hearing loss	19 (26)	4 (40)	7 (33)	8 (19)	0.26
Demographic characteristics					
White	63 (86)	7 (70)	18 (86)	38 (90)	0.29
Female	62 (84)	9 (90)	17 (81)	36 (86)	0.78
Age at symptom onset, median (IQR) years	36 (27–43)	37 (22–40)	37 (31–46)	35 (26–43)	0.36
Age at diagnosis, median (IQR) years	43 (33–52)	39 (23–49)	48 (43–56)	42 (31–50)	0.08
Diagnostic delay, median (IQR) years	5 (2–10)	1 (0.6–5)	10 (3.5–20)	4.5 (2–8.5)	0.007
Clinical symptoms					
Fever	18 (24)	2 (20)	7 (33)	9 (21)	0.55
Weight loss	8 (11)	4 (40)	0 (0)	4 (9)	0.02
Oral ulcers	22 (30)	2 (20)	10 (48)	10 (24)	0.12
Genital ulcers	12 (16)	0 (0)	7 (33)	5 (12)	0.02
Audiovestibular symptoms	57 (78)	7 (70)	16 (76)	34 (80)	0.73
Sinonasal disease	68 (94)	9 (90)	19 (90)	40 (95)	0.82
Costochondritis	63 (86)	9 (90)	17 (80)	37 (88)	0.70
Dry cough	62 (85)	10 (100)	20 (95)	32(76)	0.09
Skin involvement	19 (26)	0 (0)	0 (0)	6 (14)	0.03
Sicca symptoms	30 (41)	5 (50)	8 (38)	17 (40)	0.82
Wheezing	30 (41)	5 (50)	13 (62)	12 (28)	0.03
Stridor	10 (13)	7 (70)	0 (0)	3 (7)	<0.0001
Other diagnoses prior to RP diagnosis					
Asthma	28 (38)	5 (50)	13 (62)	12 (28)	0.009
Ear infections	9 (12)	2 (20)	1 (5)	6 (15)	0.36
Sinusitis	18 (24)	4 (40)	4 (19)	10 (24)	0.46

* Except where indicated otherwise, values are the number (%). RP = relapsing polychondritis; IQR = interquartile range.

RP had more genital ulcers (33% versus 0% in the type 1 RP subgroup and 12% in the type 3 RP subgroup; $P = 0.02$), and wheezing (62% versus 50% in the type 1 RP subgroup and 28% in the type 2 RP subgroup; $P = 0.03$). Patients with type 3 RP had significantly more skin involvement (14% versus 0% in the type 2 RP subgroup and type 1 RP subgroup; $P = 0.03$). A prior diagnosis of asthma was significantly more common in the type 2 RP subgroup (62% versus 50% in the type 1 RP subgroup and 24% in the type 3 RP subgroup; $P = 0.009$). There were no other significant differences in clinical symptoms between the subgroups (Table 1).

The 3 subgroups differed based on a few of the dynamic CT and PFT results. Patients with type 1 RP had a significantly greater prevalence of tracheal wall thickening on dynamic CT (90% versus 14% in the type 2 RP subgroup and 10% in the type 3 RP subgroup; $P < 0.0001$), and air trapping (89% versus 67% in the type 2 RP subgroup and 34% in the type 3 RP subgroup; $P = 0.002$). Compared to the other subgroups, the type 1 RP subgroup had significantly decreased forced expiratory flow, midexpiratory phase of 25–75% predicted (38% versus 88% in the type 2 RP subgroup and versus 82% in the type 3 RP subgroup; $P = 0.01$) and forced expiratory volume in 1 second/forced vital capacity % predicted (60% versus 76% in the type 2 RP subgroup and 79% in the type 3 RP subgroup; $P < 0.001$) (Table 2).

There were no statistically significant differences between the subgroups at study entry in use of synthetic or biologic DMARDs, daily prednisone requirement, or markers of inflammation. Microcytic anemia was significantly more common in patients with type 1 RP (20% versus 0% in the type 2 RP subgroup and 2% in the type 3 RP subgroup; $P = 0.02$).

DISCUSSION

RP is a potentially severe, debilitating, and in some cases, fatal disease that can be difficult to diagnose due to heterogenous disease manifestations. In this study, 3 clinical subgroups of RP were identified based on overall patterns of disease using data-driven approaches. Although all of the patients met diagnostic criteria for RP, clinical patterns of the disease varied considerably. Only a minority of patients (14%) had a pattern of disease considered classic for RP (type 1 RP), with ear chondritis and extensive damage to the cartilage of the nose and upper airway.

Table 2. Differences in imaging, pulmonary function test findings, treatment, and outcomes among the 3 subgroups of patients with RP*

	All patients (n = 73)	Type 1 RP (n = 10)	Type 2 RP (n = 21)	Type 3 RP (n = 42)	*P*
Chest dynamic CT scan					
Airtrapping, no. (%)	35 (51)	8 (89)	14 (67)	13 (34)	0.002
Tracheal wall >3 mm, no. (%)	16 (22)	9 (90)	3 (14)	4 (10)	<0.0001
Pulmonary function tests					
FVC % predicted	91 (83–101)	94 (58–102)	90 (81–103)	91 (85–100.5)	0.92
FVC, liters/second	3.3 (2.8–3.8)	2.9 (1.9–3.2)	3.3 (2.4–3.8)	3.4 (3–3.9)	0.12
FEV_1 % predicted	85 (75–96)	76 (26–84)	83 (67–97)	89 (81–89)	0.06
FEV_1, liters/second	2.4 (2–3)	1.34 (0.7–2.3)	2.3 (1.9–2.9)	2.75 (2.3–3.1)	0.01
$FEF_{25–75}$ % (reference)	80 (51–94)	38 (15–66)	88 (47–92)	82 (65–97)	0.01
$FEF_{25–75}$, liters/second	2.32 (1.49–2.85)	0.9 (0.4–1.7)	1.98 (1.4–2.5)	2.58 (2–3)	0.01
FEV_1/FVC %	76 (72–80)	60 (43–71)	76 (66–80)	79 (75–81)	0.0006
VC % (reference)	95 (86–107)	91 (44–102)	94 (86–111)	96 (87–107)	0.55
VC, liters/second	3.34 (2.86–3.99)	3 (1.42–3.2)	3.1 (2.7–3.8)	3.46 (3.1–1.4)	0.04
TLC, % (reference)	93 (87–101)	92 (66–97)	94 (87–105)	93 (89–99)	0.78
TLC, liters/second	4.8 (4.2–5.4)	4.7 (4.5–5.3)	4.7 (4–5.7)	4.9 (4.2–5.4)	0.7
RV % (reference)	74 (61–86)	75 (51–101)	82 (66–97)	74 (61–83)	0.36
RV, liters/second	1.36 (1.1–1.5)	1.5 (1.4–2.7)	1.4 (1.1–1.6)	1.2 (0.9–1.5)	0.06
RV/TLC (reference)	77 (68–88)	80 (65–104)	87 (71–95)	72 (64–85)	0.12
$DLco_{adj}$ %	18 (17–22)	18 (15–19)	18 (17–22)	19 (17–21)	0.25
$DLco_{adj}$	68 (64–74)	66 (61–70)	67 (64–80)	69 (61–74)	0.61
Physician global assessment	3 (2–4)	3 (2–4)	4 (3–5)	5 (3.75–6)	0.0003
Treatment					
Current prednisone dosage	7 (0–20)	10 (5–20)	7.5 (0–25)	5 (0–20)	0.69
Synthetic DMARDs, no. (%)	49 (67)	8 (80)	16 (76)	25 (59)	0.25
Biologic DMARDs, no. (%)	32 (43)	7 (70)	8 (38)	17 (40)	0.19
Complications					
Tracheostomy, no. (%)	7 (1)	5 (50)	0 (0)	2 (5)	0.0003
Disability, no. (%)	25 (34)	2 (20)	12 (57)	11 (26)	0.10
ICU admission, no. (%)	12 (16)	5 (50)	2 (9)	5 (12)	0.02
Markers of inflammation					
CRP, mg/dl	2.4 (0.8–8.6)	4.7 (0.37–12.5)	3.9 (1.25–8.1)	2 (0.77–0.52)	0.568
ESR, mm/hour	11 (6–20)	13.5 (3.5–54.5)	9 (6.5–20)	11.5 (6–19.5)	0.974

* Except where indicated otherwise, values are the median (interquartile range). RP = relapsing polychondritis; CT = computed tomography; FVC = forced vital capacity; FEV_1 = forced expiratory volume in 1 second; $FEF_{25–75}$ = forced expiratory flow, midexpiratory phase; VC = vital capacity; TLC = total lung capacity; RV = residual volume; $DLco_{adj}$ = diffusing capacity for carbon monoxide adjusted for hemoglobin or other factor(s); DMARDs = disease-modifying antirheumatic drugs; ICU = intensive care unit; CRP = C-reactive protein; ESR = erythrocyte sedimentation rate.

These patients, perhaps not surprisingly, had the fastest time to diagnosis, yet still experienced a median diagnostic delay of 1 year. The other 2 subgroups of patients were characterized by either lower airway–predominant disease (type 2 RP) or disease in the absence of overt cartilage damage (type 3 RP). Interestingly, patients with predominantly lower airway involvement had the lowest prevalence of ear involvement and experienced diagnostic delays of 10 years on average. RP can be a devastating condition, particularly when patients develop cartilage damage due to untreated inflammation (11–14). Recognition of a wider range of disease patterns in RP and development of disease-specific assessment tools may facilitate diagnosis and earlier medical intervention, which may, in turn, prevent the development of permanent damage (15).

Findings from this study emphasize that patients with RP have a high burden of serious disease-related complications. Damage to critical cartilaginous structures was common, including tracheomalacia, bronchomalacia, subglottic stenosis, ear cartilage damage, and saddle-nose deformity. Many patients required admission to the ICU or developed disabilities. Despite aggressive treatment with DMARDs, biologics, and glucocorticoids, all the patients had persistently active disease at initial evaluation. Even patients with type 3 RP without overt cartilage damage reported a high rate of disability and had active disease despite treatment. Both timely intervention and more effective treatments are needed for this condition.

Other investigators have defined subgroups in RP based on clinical patterns of disease. Shimizu et al compared clinical features in 239 patients with RP based on auricular involvement, respiratory involvement, and overlap of auricular and airway involvement (16). Accordingly, the present study confirms, using unbiased analytical approaches, the presence of a group of patients with RP who have predominant airway disease. Dion et al (3) retrospectively analyzed 142 patients over a 12-year period.

Cluster analysis was used to identify 3 subsets of patients defined by associated hematologic disease (n = 12), respiratory

predominant disease (n = 37), or mild disease (n = 93) (3). Patients with associated hematologic disease, defined mostly by myelodysplastic syndromes, were older, typically male, and had the most severe phenotype, with a mortality rate of 58% and an ICU admission rate of 50%. In this study, there were a few patients with hematologic abnormalities, including anemia and elevated mean corpuscular volume; however, none of these patients met the diagnostic criteria for myelodysplastic syndrome. In these patients, cartilaginous involvement was limited to the ear, nose, and joints without evidence of damage, such as saddle-nose deformity or tracheobronchomalacia; therefore they were classified in the type 3 RP group. Patients with respiratory predominant disease identified in the study by Dion et al were younger, had tracheobronchial and laryngeal involvement with abnormal functional respiratory tests, were most likely to receive biologic therapy, and had the highest rate of ICU admissions. Although a group with predominantly lower airway disease (type 2 RP) was also identified in the present study, these patients were the oldest and had the longest time to diagnosis, suggesting that this subgroup perhaps is the most difficult to recognize. In this study, a higher prevalence of tracheomalacia (43%) was observed than was observed in the study by Dion et al (22%), potentially because every patient underwent dynamic CT scan of the chest to evaluate for airway involvement, per study protocol.

The last subgroup described by Dion et al was classified as having a mild phenotype defined by an absence of severe tracheobronchial involvement or hematologic disease, low mortality, infrequent ICU admissions, and increased likelihood of achieving sustained clinical remission. In the present study, a similar group was identified and called type 3 RP. Although patients in this group lacked evidence of significant cartilage damage, this group did not have mild disease as seen by Dion et al. Patients with type 3 RP had a high frequency of disability (26%), hearing loss (19%), and active disease despite the use of DMARDs (60%) and a maximum daily prednisone dosage of ≥60 mg in 45% of these patients. Differences in study design could explain some of the differences between the results of the present study and those of previous studies. Unlike the study by Dion et al, which was retrospective and subject to assessment bias, patients in the present study were evaluated in a prospective cohort and underwent comprehensive standardized clinical assessment including direct laryngoscopy, dynamic CT imaging of the airways, PFTs, and audiometry testing. Additionally, the present study employed standardized definitions of disease features and a different statistical analytical method than prior studies.

Some potential study limitations should be considered. This study cohort was smaller than has been previously evaluated in studies that have attempted to define subgroups within RP; however, RP is a rare disease and this study represents the first prospective cohort study where every patient underwent standardized clinical assessment under a research protocol. No differences in mortality or treatment response were identified between the subgroups, possibly due to the fact that the analysis was done using only data from the initial study visit. Future longitudinal studies from the cohort may be required to identify differences in clinical outcomes among patients with RP. This study was not an inception cohort. It is possible that partitioning strategies using data collected at the time of diagnosis could identify different subgroups of patients and that a patient could change subgroup status over time. Further research is needed to evaluate whether biologic differences underlie this clinical classification scheme.

In conclusion, this study used latent class analysis to identify 3 subgroups of patients with RP that differed in clinical and radiographic characteristics of disease, time to diagnosis, and disease-related complications. Future studies should investigate whether subgroups of patients with RP also differ in terms of causal factors such as genetic risk or environmental exposures, immunologic mechanisms of disease, and responses to treatment. Despite differences in the clinical spectrum of disease, patients with RP commonly experience long diagnostic delays, inadequate clinical response to therapy, and substantial morbidity. Findings from this study underscore a tremendous unmet need for clinical advancement in this potentially devastating and under-studied disease.

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AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Ferrada had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Ferrada, Grayson.

Acquisition of data. Ferrada, Rimland, Quinn, Sikora, Kim, Allen, Sirajuddin, Goodspeed, Chen, Grayson.

Analysis and interpretation of data. Ferrada, Grayson.

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