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Relapsing polychondritis: Best Practice & Clinical Rheumatology

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A B S T R A C T

Relapsing polychondritis (RP) is an uncommon inflammatory disorder that predominantly targets cartilaginous structures. The disease frequently affects the nose, ears, airways, and joints, but it can also impact organs that aren't primarily cartilage-based, such as blood vessels, skin, inner ear, and eyes. Given its infrequent occurrence and recurrent symptoms, patients often experience delays in proper diagnosis. Lately, based on the organs involved, the disease's diverse manifestations have been categorized into specific clinical groups, based on the most likely organ involvement including auricular, nasal, pulmonary, and musculoskeletal. More recently the discovery of a new disease, called (Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic) VEXAS syndrome, due to mutations in *UBA1* gene, identified the cause of 8 % of the patients with a clinical diagnosis of RP. VEXAS is likely the cause of a previously described “hematologic subgroup” in RP. This discovery is proof of concept that RP is likely more than one disease (Beck et al., Dec 31 2020; Ferrada et al., 2021).

People diagnosed with RP face numerous hurdles, with the quality of their lives and overall prognosis being affected. Diagnosing the condition is particularly challenging due to its fluctuating symptoms, the absence of specific markers, and the lack of universally recognized classification criteria. For a correct diagnosis, it's

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imperative for healthcare professionals to identify its unique clinical patterns. Moreover, there are no approved metrics to gauge the disease's severity, complicating patient management.
This review seeks to equip clinicians with pertinent insights to better diagnose and attend to these complex patients.

Introduction

Relapsing polychondritis (RP) is a rare systemic inflammatory disease that primarily affects cartilaginous structures in the body. Commonly involved organs include the nose, ears, airway, and joints. However, it can also affect organs not rich in cartilage, such as the vasculature, skin, inner ear, and eyes. Due to its rarity and relapsing nature, diagnosing, and treating RP can be challenging, leading to delays in appropriate care. Recently, the disease's phenotypic heterogeneity has been categorized into clinical subgroups based on affected organ systems, such as the auricular, nasal, pulmonary, and hematologic subgroups. These classifications help determine the unique natural history and outcomes associated with these subtypes.

Diagnosing RP relies on clinician knowledge and recognition of the pattern of organ involvement, which can be difficult due to the disease's rarity and systemic nature. As a result, patients with RP may initially seek help from various specialists, including rheumatologists, otolaryngologists, and pulmonologists. It's crucial for all specialists to familiarize themselves with the features of RP to ensure timely and accurate diagnoses.

There are currently no FDA-approved therapies for RP, and clinical trials to guide management are limited. Due to variations in disease severity and organ involvement, treatment approaches should be tailored to each patient, considering the specific organs affected and the extent of inflammation.

With this review we hope to provide general knowledge about the disease, organ assessment, and treatment recommendations.

Epidemiology

The epidemiological data in RP is somewhat limited compared to more common diseases. Although RP has been described worldwide, as with many rare diseases, the prevalence may be underreported in areas with limited access to healthcare or specialized medical services. Therefore, the exact prevalence of RP worldwide is not well-established.

Data from the Mayo clinic in the 1980's found that the incidence of RP was 3.5 cases per million in United States [3]. While widely cited, the original epidemiologic study generating this data could not be identified after a thorough review of the literature [4–6]. More recent studies have demonstrated a much lower incidence; however, these have been performed in different populations. A study from the United Kingdom reported an incidence of 0.71 cases per million patients per year from 1990 to 2012 utilizing data from the Clinical Practice Research Datalink, a nationally representative sample of patients [6]. Read Codes were used to identify 117 RP patients and a limited validation was performed using a questionnaire with 50 of the 61 responses confirmed [6].

The largest epidemiological study performed was an analysis of Hungarian billing records from 2002 to 2013 which identified 256 cases in 124 million patient-years [7]. While they did not provide an incidence, it can be estimated at 1.8 cases per million patients per year based on the published data. The patients in this sample were identified using ICD-10 diagnosis codes and medication purchases. No post-hoc validation study was performed [7].

Additional case series from the United States, Japan, China, and India have provided some insight into age, ethnicity, and gender. The average age of onset in all studies was between 40 and 60 years of age; however, there are reports of pediatric cases and the age range at disease onset was 4–93 years. There's no clear predilection for any specific ethnic group. Studies in different populations report a

roughly similar prevalence. However, comprehensive epidemiological studies across different ethnic groups are lacking.

There is a slight female predominance, with most studies indicating that around 60–70 % of RP patients are female [8,9].

The mortality rate of patients with RP varies. Some studies have suggested that the 5-year survival rate is around 90 %, but this can vary based on factors such as the severity of respiratory or cardiac involvement and access to treatment [8].

The leading causes of death in RP patients include complications related to airway involvement, cardiovascular complications, infections (possibly related to immunosuppressive treatment), and other organ system complications.

Clinical manifestations

Patients with relapsing polychondritis can have a combination of clinical manifestations depending on affected organs. Because the disease is rare it has been difficult to identify and describe in more detail the full range of clinical manifestations. The most common organs involved in the disease are cartilaginous structures such as the ears, nose, airway, and joints. However, the spectrum of clinical symptoms associated with these organs is not well defined.

We will divide the clinical manifestations in two categories, cartilaginous structures, and no cartilaginous structures.

Cartilaginous structures

Ears

The most distinguishing hallmark of RP is auricular chondritis and this is present in approximately 90 % of patients with RP although it may not be present at disease onset [10]. When presenting in isolation or unilaterally, it is important to distinguish it from alternative diagnoses. The differential for a "red ear" is broad and includes infections, common and rare skin disorders, and skin findings in association with neoplasia. Infection of the external ear, otitis externa, can result from a fungal, viral, or bacterial infection such as syphilis, leprosy, tuberculosis, herpes zoster. Importantly, *pseudomonas* which can be necrotizing and progress rapidly should be suspected in patients with recent exposure to water such as pools and in patients with associated risk factors including a history of diabetes mellitus [11]. Alternatively, non-infectious causes include equally rare diseases such as chondrodermatitis nodularis helicis and the appropriately named red-ear syndrome [12,13] Common environmentally triggered causes such as sunburn and frost bite may be readily identified on history. To decide if a patient is having ear chondritis, is important to know the onset, associated symptoms as well as exposures. For example, patients with red ear syndrome have associated headaches, whereas infection should be suspected in patients with previous exposures.

Nose

Nose chondritis is observed in approximately 60 % of patients during the disease [14], and characterized by pain of the nasal bridge area. This usually occurs without other visible inflammatory signs. Relapsing nasal chondritis can lead to destruction of the cartilage leading to the classic saddle nose deformity. Differential diagnosis includes vestibulitis, and it can be differentiated from chondritis by the location. Vestibulitis is usually located around the nostrils, in conjunction with erythema and swelling and sometimes a pustule or drainage. Patients with suspected vestibulitis will need emergent evaluation by ENT and possibly imaging such as MRI or CT scan to ruled out deep tissue involvement.

Neck cartilage

Different cartilaginous structures are present within the neck including the thyroid cartilage, which is a large cartilaginous structure located in the anterior neck, leading to anterior cervicalgia aggravated by palpation, which can be mistaken for De Quervain thyroiditis. These attacks can be severe resulting in an acute presentation to an emergency department [15,16].

These cartilages can get affected in patients with RP and is difficult to assess because of the location outside the airway, therefore is not easily visualized and radiologic studies are also difficult to detect inflammation because of the thinness of this anatomic structure.

Respiratory system. Cartilage is present in multiple respiratory structures and respiratory manifestations are common in RP because of cartilaginous inflammation or damage. There is cartilage in the firm but flexible tissue along the airways from the nasal cavity down to the respiratory bronchioles.

Chondritis further along respiratory tree is an important cause of morbidity and mortality in RP, affecting about 30–50 % of patients during the course of the disease [14]. Laryngeal chondritis manifests as a dry cough, with dysphonia or even aphonia secondary to edema and/or vocal cord paralysis. Stridor can occur in the case of glottic inflammation or subglottic stenosis.

Tracheobronchial involvement is associated with some of the most serious complications of RP, and screening is critical when RP is suspected. It can be a presenting symptom of up to 10 % of patients but eventually develops in approximately half of all patients diagnosed with RP [10,17]. Airway damage due to recurrent untreated inflammation can lead to tracheal and/or bronchial thickening or collapse. Because symptoms of patients with lower airway involvement can be unspecific, including dry cough, dyspnea and intermittent episodes of wheezing, these patients very often have a diagnosis of difficult to treat adult-onset asthma at the time RP diagnose.

Indications for bronchoscopy, biopsy or intubation must be carefully considered, as there is an increased risk of perforation or of triggering a flare-up in the event of an invasive procedure.

Although pulmonary infiltrates can be seen in patients with RP, it is more common in patients with a diagnosis of VEXAS [18].

Chest wall

Cartilage in the chest wall is in the tissue between the ribs and the sternum as well as the ends of the floating ribs.

Inflammation of the cartilaginous tissues of the ribs, known as costochondritis, is exquisitely painful and can cause a restrictive ventilatory defect. This manifestation is highly suggestive of RP and must be considered in cases of relapsing Tietze syndrome, described by NORD as “a rare, inflammatory disorder characterized by chest pain and swelling of the cartilage of one or more of the upper ribs (costochondral junction).”

Costochondritis can be so severe that will prompt patients to go to the ER. (ref survey paper).

Joints

Joint involvement is common in RP ($\approx$65 % of patients) and can frequently be mistaken for seronegative RA. Inflammatory arthralgia is more frequent than true arthritis, but inflammatory oligoarthritis and rarely polyarthritis can be seen. Joint symptoms often present with an intermittent asymmetric pattern involving small and large joints, sometimes appearing migratory. In the absence of concomitant rheumatoid arthritis, joint involvement in RP is seronegative, non-erosive, and non-deforming.

The most common joint affected in children is the knees and ankles [19].

Axial involvement, particularly of the cervical or lumbar spine, can occur with RP but this should raise suspicion for an associated spondylarthritis, particularly, if there are compatible radiological findings in an HLAB27+ patient. Other rheumatological manifestations such as tendonitis, tenosynovitis, or other periarticular involvement may occur.

Non-cartilaginous organ involvement

Eyes

Ocular involvement is common (occurring in about 50 % of patients) and may precede the onset of chondritis by several years [20]. The most frequent manifestations are episcleritis and scleritis [21,22]. The latter is the most serious ocular diagnosis as it can result in scleromalacia and increase risk of perforation of the globe. Other conditions encountered are, in order of frequency, simple or ulcerated

keratoconjunctivitis sicca (sometimes associated with Sjögren's syndrome), uveitis, retinal damage, and optic nerve damage, which may progress to true optic nerve atrophy.

Cardiovascular system

Cardiac involvement is less common, occurring in approximately 7.1 % of patients [23]. Cardiac involvement occurs predominantly in male patients, late in the course of the disease, and can be associated with a more severe disease phenotype [24]. It currently represents one of the major causes of mortality. The tissue of the endocardium as well as the walls of the vessels may be involved manifesting as a vasculitis. Valvopathy, occurring in approximately 10 % of patients during disease, typically involves the aortic valve causing insufficiency due to ring dilatation (in 4–6% of patients). Mitral insufficiency is seen less commonly (2–4% of patients). Valvular insufficiency typically follows a progressive clinical course requiring valvuloplasty or valve replacement. Valvopathy should prompt further screening for an associated aortic aneurysm. Aneurysms very rarely extend to distal arterial vessels and the abdominal aorta [25–27].

Additional cardiovascular complications can include pericarditis or vasculitis of the medium (including coronary arteries) and small vessels. According to Michet et al. [24], 5–14 % of patients present with cutaneous leukocytoclastic vasculitis and 10 % with systemic microvascular involvement and are responsible for peripheral and central neurological complications. More rarely, large vessel vasculitis has been reported [28,29]. The increasing use of PET/CT may facilitate early diagnosis of this rare manifestation associated with significant morbidity and mortality [30].

Large vessel vasculitis should be suspected in patients with associated Bechet's disease symptoms, such as mouth and genital ulcers, which is currently recognized as Mouth, and Genital Ulcers with Inflamed Cartilage (MAGIC) syndrome [31].

Skin

Skin involvement is polymorphic and non-specific [32], occurring in about 1/3 of patients during the disease. Oral aphthous ulcers, nodules of the upper or lower limbs, purpura, papules, aseptic pustules, superficial phlebitis, livedo reticularis, ulcerations of the limbs, necrosis of the extremities, neutrophilic dermatoses including Sweet's syndrome or erythema elevatum diluvium lesions, urticaria, and angioedema have all been described [32].

Skin involvement, and more particularly neutrophilic dermatosis, seems to be associated with patients with VEXAS and a clinical diagnosis of relapsing polychondritis (VEXAS-RP) [18,33], thus skin involvement in presence of chondritis should prompt systematic investigation for underlying myelodysplasia and VEXAS, especially in older patients.

Neurological system

Neurological manifestations are rare and mainly involve the central nervous system in the form of cranial nerve damage. Other manifestations have been described and are like those encountered in cerebral vasculitis (focal deficits, epilepsy, aseptic lymphocytic meningitis, limbic encephalitis). Peripheral neuropathy may be seen in some cases with associated vasculitis [34].

Renal involvement

Renal involvement specific to RP remains truly exceptional (<2 % of patients during the disease) and controversial and should prompt consideration of an alternative diagnosis such as GPA or microscopic polyangiitis (MPA) [35,36].

Diagnosis

Since the underlying pathogenesis and inflammatory mechanisms remain unknown for RP, there are no pathognomonic, sensitive, or specific tests to confirm the diagnosis of RP. Therefore, the diagnosis remains based on clinical findings, with the support of laboratory and imaging studies.

The diagnostic criteria for RP, as establish by McAdam's [10] and modified by Damiani and Levine [37], involve assessing the involvement of multiple organ systems.

To meet the McAdam's criteria the patients must have at three out of the following six organs:

1. Bilateral auricular chondritis
2. Nonerosive, seronegative inflammatory polyarthritis
3. Nasal chondritis
4. Ocular inflammation (conjunctivitis, keratitis, scleritis/episcleritis, uveitis)
5. Respiratory tract chondritis (laryngeal and/or tracheal cartilages)
6. Cochlear and/or vestibular dysfunction (neurosensory hearing loss, tinnitus, and/or vertigo)

These criteria were further modified by Damiani and Levine to account for variability in presentation timing and findings and include histologic confirmation, which is not commonly used in clinical practice. The Damani and Levine's criteria is as follows:

1. Having 3 or more criteria
2. One or more of the clinical findings included in the McAdam criteria, with positive histologic confirmation.
3. Chondritis at two or more separate anatomic locations with a response to glucocorticoids and/or dapsone.

Although these criteria provide a framework, the diagnosis of RP is primarily made based on clinical findings, and additional laboratory and imaging studies may be used to support the diagnosis. It is important to consult with a healthcare professional for a thorough evaluation and appropriate management.

It is critical for providers and patients to understand that, at first evaluation, there may be an incomplete presentation of the disease and continued close follow-up is warranted with consideration of a trial of glucocorticoids. An auricular biopsy is of limited benefit in the routine evaluation but may help in certain circumstances such as for patients with unilateral ear symptoms, lack of multi-system involvement, and/or a poor response to steroids. The benefit being to “rule in” alternative diagnoses rather than RP.

Physical examination

The intermittent nature of relapsing polychondritis (RP) makes it challenging to diagnose based on a single clinical encounter. Since episodes of inflammation can be transient, having a chronology of symptoms through patient documentation and photographs can be extremely valuable.

Photographs of ear chondritis taken by the patient during flare-ups can be especially useful. They can show the progression of inflammation, redness, and possible deformities over time. Similarly, pictures of joint swellings, especially if they are intermittent, can assist in the diagnostic process and in assessing disease activity.

Given the relapsing nature of the disease, a detailed history, including the chronology of symptoms, frequency of flare-ups, and any triggers noticed by the patient, can be invaluable.

Patient's own notes, diaries, or symptom logs can provide additional context and details that may be missed during routine clinical encounters.

While auricular chondritis is often the most common clinical examination finding in RP, occurring in up to 90 % of cases throughout the disease progression, it is important to note that there is currently no clear definition of ear chondritis [14,38,39]. Additionally, it is worth mentioning that this symptom may manifest later in the course of the disease. Therefore, relying solely on ear chondritis for diagnosis can potentially lead to delays in diagnosing RP.

Given the absence of a clear-cut definition of ear chondritis, paying attention to the patient's description of their symptoms becomes crucial. Pain is an important symptom, often indicative of inflammation. The experience of pain is subjective and varies from person to person; what might be described as mild discomfort by one patient might be intense pain for another. Patients who live with

RP often become attuned to their body's responses and can provide valuable insights about the onset, progression, and resolution of their chondritis episodes.

Episodes of chondritis can last from an hour to days and weeks and can spontaneously regress. Since the definition of ear chondritis is not available, we suggest interpreting the patient's symptoms as the main tool to decide if the etiology is inflammatory.

Nasal ulcers, especially those located on the anterior part and around the nasal septum, can be indicative of nasal cartilage inflammation. They may also serve as a marker of disease activity.

Respiratory assessment, including listening to the lungs and assessing for stridor can provide clues about further emergent needed evaluations including ENT.

Laboratory testing

Routine laboratory monitoring for disease complications including a complete blood hemogram to assess for changes in white blood cell number such as leukocytosis, neutropenia, lymphopenia, as well as anemia and thrombocytopenia. Various types of anemia can be associated with RP more commonly anemia of chronic disease, and iron deficiency. Additionally, complete blood counts are essential in the monitoring and assessment of bone marrow dysfunction which can occur because of immunosuppressive therapy or in patients with Vacuoles, E1 enzyme, X linked, Autoinflammatory, Somatic (VEXAS) syndrome.

Standard chemistry laboratory evaluation to assess electrolytes, kidney function, liver function, and for evidence of hemolysis is routinely performed depending on the clinical presentation. Inflammatory markers, such as C-reactive protein (CRP) and the erythrocyte sedimentation rate (ESR) can be measured; however, many patients presenting with clinically significant inflammation have normal values. Normal CRP and ESR levels are not sufficient to exclude active disease and may not be helpful in diagnosing RP.

Other diagnostic testing

Though the diagnosis is clinical, ancillary testing modalities are important to establish the extent of organ involvement, monitor response to therapy, and to monitor for the development of complications.

Pulmonary function test: The main reason to obtain pulmonary function tests (PFTs) in patients with RP is to rule out other associated conditions, such as asthma. PFTs should not be used to diagnose airway disease or follow disease activity as changes in airway loops are found in advanced disease.

Dynamic chest CT scan: Patients with suspected or diagnosed RP should be evaluated by dynamic chest CT for airway involvement, including tracheomalacia, tracheal thickening (>2 mm) or calcification. Chest CT scans with inspiratory and expiratory images must be obtained to diagnose tracheomalacia.

Laryngoscopy: Patients with suspected airway disease should be evaluated by an experienced otolaryngologist if possible. If the patient has stridor, an urgent ENT evaluation is warranted.

Audiology: Any patient with suspected or diagnosed RP should undergo audiometry. Audiometric assessments should be performed periodically at follow up visits and if new symptoms are present.

Echocardiogram: Patients with RP can rarely develop valvulitis. Since echocardiogram is a noninvasive test, it is prudent to perform this study for screening purposes.

Fluorodeoxyglucose positron emission tomography/computed tomography (FDG-PET/CT)

In patients with associated conditions like MAGIC syndrome (Mouth and Genital Ulcers with Inflamed Cartilage), the risk of vascular involvement increases, and FDG-PET/CT can serve as an invaluable tool. While FDG-PET/CT can be invaluable, it's not without limitations. Physiological uptake of FDG in certain tissues, artifacts, or non-specific uptake can sometimes challenge the interpretation. It's also a more expensive modality with exposure to radiation. Hence, its use should be based on individual patient needs, clinical presentation, and the suspected extent of disease involvement.

Ear biopsy: Data from ear biopsies is based on case reports, and although it may provide a general understanding of the immunopathology of RP, it is difficult to apply to clinical practice. Given the invasive nature of biopsies and the potential risks, coupled with the fact that diagnosis can often be made based on clinical manifestations, laboratory tests, and imaging, a biopsy is generally reserved for unclear cases or when a differential diagnosis needs exclusion. It's also noteworthy to mention that while the biopsy offers valuable information on the disease process, it doesn't necessarily change the management or prognosis of RP in a significant way for most patients.

Phenotypic grouping

Different groups studying RP have recognized the heterogeneity of the disease and utilized different methodologies to identify clinical subgroups. Interestingly, a respiratory subtype was identified in all studies, demonstrating that patients with airway involvement may be distinct from other patients. Another important aspect of identifying these subgroups is the different outcomes, response to treatment, and complications.

French RP cohort of Dion et al.

Dion et al. retrospectively analyzed a French cohort of 142 RP patients over a 12-year period, and described 3 different phenotypes using cluster analysis [14]. The first and more frequent phenotype (65 %) was mainly characterized by episodes of relapsing minor chondritis, whereas the second (26 %) was characterized by respiratory involvement, and the third (9 %) by hematological manifestations (recently associated in most cases with VEXAS syndrome) [8].

First phenotype: "mild phenotype"

The most frequent phenotype of RP is characterized by relapsing episodes of minor chondritis of the auricular cartilage and nasal bridge and portends a better prognosis. The classical chondritis seen in this phenotype facilitates diagnosis of RP.

Second phenotype: respiratory predominant involvement

This phenotype is characterized by chondritis of the laryngo-tracheo-bronchial tree, one of the more severe manifestations of the disease which can lead to death in some cases.

Third phenotype: hematological involvement and VEXAS syndrome

Cluster analysis of patients with RP isolated a particular phenotype with the worst prognosis, in which men over 60 years were over-represented and presented with hematological anomalies (myelodysplastic syndrome in most cases). Cardiac involvement was also more frequent in this phenotype. This phenotype was more recently identified as VEXAS syndrome.

NIH RP cohort of Ferrada et al.

Ferrada et al. prospectively analyzed 73 patients of the RP cohort of the NIH [40] and identified three different phenotypes. The first subgroup was more rapidly diagnosed due to a"classic phenotype" with ear chondritis and extensive cartilage damage to nose and upper airway cartilages (Type 1 RP). The other phenotypes were defined by lower-airway predominant disease (Type 2 RP) or absence of cartilage damage (Type 3 RP). A few patients categorized as type 3 RP presented with limited cartilaginous involvement (ear, nose, and joints) and hematologic abnormalities including anemia and elevated MCV, but none met the diagnostic criteria for myelodysplastic syndrome (MDS). Skin involvement was also only described in type 3 RP. In contrast to Dion et al. there were no differences in

epidemiological patient characteristics (geographical origin, gender, age at symptom onset, age at diagnosis) and disease duration between the identified subgroups in this series.

Japanese RP cohort of Shimizu et al.

Shimizu et al. [41] compared clinical features in 239 RP patients. The subgroups were defined prior to the analysis. The subgroups included auricular involvement (A group) defined as inflammation of the external ear, respiratory involvement (R group) defined as saddle nose deformity and large airway disease, and progressive disease and overlap of auricular and airway involvement (O group). These three subgroups had different associated characteristics and disease progression.

RP-VEXAS

VEXAS syndrome (Vacuoles, E1 enzyme, X linked, Auto-inflammatory, Somatic) is a new auto-inflammatory syndrome first described in December 2020 [1]. It is due to somatic mutations of the *UBA1* gene restricted to myeloid progenitors. VEXAS is characterized by myeloid-driven systemic inflammation and associated with bone marrow failure. Estimated prevalence of *UBA1* pathogenic variants was 1 in 13,591 across all age groups in a recent retrospective observational study of the Geisinger cohort, an American cohort of patients [42]. Prior to identification of this new disease, patients now known to have VEXAS syndrome were diagnosed with numerous inflammatory diseases and were characterized by resistance to conventional therapy and poor prognosis. In the initial description of VEXAS syndrome, 60 % of the patients met established diagnostic criteria for RP [1]. Chondritis in VEXAS might be less frequent than initially believed as a recent study found no RP-manifestations in the Geisinger American cohort [42]. In retrospect, patients of the third phenotype in the French cohort of Dion et al. [14] may have had RP associated with VEXAS syndrome (VEXAS-RP) and this may also be the case for the subgroup of patients with type 3 RP in the American RP cohort at the NIH [40]. In a more recent study, Ferrada et al. [33] prospectively screened 92 patients in the NIH RP cohort for somatic mutations of *UBA1* and detected a mutation in 7.6 % patients. These patients presented with less severe cartilage involvement limited to the ear and nose without any cartilaginous damage or involvement of the large airways, and commonly presented with an infiltrative inflammatory disease of the lungs and thromboembolic complications. These findings were confirmed by Khitri et al. [18] who compared clinical characteristics of VEXAS-RP and idiopathic RP in patients of the retrospective French cohort and found a more inflammatory disease (greater prevalence of fever and higher median C-reactive protein levels) with a higher prevalence of ocular involvement, skin lesions, pulmonary infiltrates, and cardiac involvement. In both studies, patients were more often refractory to standard RP therapy leading to further complications and death. Screening for *UBA1* mutations should strongly be considered if the patient is male and has an MCV >100 fL or platelet count <200 k/uL [2].

MAGIC syndrome

Mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome is an extremely rare entity first described in 1985 in patients presenting with clinical overlap of manifestations of both RP and Behçet's disease (BD) [31]. Existence of MAGIC syndrome as a distinct disease or an overlap syndrome remains controversial in part due to the absence of a well characterized definition.

In 2022, Luo et al. [31] described 13 patients (14 %) with MAGIC syndrome out of the 96 patients in a prospective cohort of RP at the NIH. MAGIC was defined based on the presence of recurrent oral and genital ulcers and chondritis. Interestingly, no patients with VEXAS-RP were clinically diagnosed with MAGIC syndrome. These 13 patients were pooled with 27 other patients identified from a systematic review in 4 different databases. Out of the 40 identified patients, most of the patents were female ($n = 28$; 70 %) and median age at diagnosis was 38 years (IQR 29–43 years). There was no significant difference in terms prevalence of chondritis manifestations, clinical outcomes, death, and treatment exposure between patients with RP with and without MAGIC syndrome. Compared to RP, patients with MAGIC syndrome had a greater prevalence of mucocutaneous ulcers, inflammatory eye disease (anterior uveitis, panuveitis, retinal vasculitis, 28 % vs 4 %, $p < 0.01$), BD-related cutaneous

manifestations (erythema nodosum, pseudofolliculitis, and pathergy, 35 % vs 1 %, $p < 0.01$), venous thromboembolism; and more systemic features such as aortitis (23 % vs 1 %, $p < 0.01$) (instead of pulmonary artery aneurysm), gastrointestinal disease (23 % vs 4 %, $p < 0.01$) and CNS involvement (8 % vs 0, $p = 0.04$). Raynaud phenomenon was described in 54 % patients of the NIH cohort.

The definition of MAGIC syndrome has been proposed to include fulfillment of either the McAdams or Damiani criteria for RP and the International Criteria for Behçet Disease (ICBD) criteria for BD (100 % sensitivity and 100 %) specificity for classifying MAGIC syndrome in the NIH cohort, excellent sensitivity in cases reported in the literature (96 %) and in the pooled cohort of 40 patients with MAGIC syndrome (98 %). Validating this definition in prospective studies might help reduce diagnostic delay of patients with MAGIC syndrome, which seems to be a common, but currently underrecognized, clinical subset within the RP population.

Treatment

Optimal treatment approaches in RP remain poorly defined. Apart from the French therapeutic guidelines carried out with the help of the French Rare Autoimmune and Auto-inflammatory Diseases Health network (FAI2R) [13] and clinical practice guidelines written under the framework of the European Reference Network on Rare and Complex Connective Tissue and Musculoskeletal Diseases (ERN ReCONNET) [43], no other official recommendations have been published to date.

Most current therapies stem from research and recommendations for other auto-immune disorders and include use of NSAIDs, glucocorticoids, DMARDs, and biological monoclonal antibodies targeting a milieu of molecular receptors such as TNF-alpha and IL-6. The primary goals of treatment in RP are to control disease activity and to avoid accrual of damage, which is associated with significant impairment in quality of life. Efficacy of treatment must be weighed against treatment-related adverse effects and complications.

Systemic glucocorticoids are often very effective and are indicated as the first line treatment in cases of severe or life-threatening organ involvement (ophthalmological, laryngeal/tracheal/bronchial, cardiac, recent-onset inner ear involvement or associated systemic large to small vessel vasculitis). Depending on the extent of involvement, the steroid dose can vary from 0.25 to 1 mg/kg/day prednisone equivalent. In the most severe cases, pulse dose intravenous glucocorticoid infusions (500–1000 mg methylprednisolone for up to 3 days) can be administrated. There are no recommendations concerning induction treatment regimen or duration of steroid therapy.

Non-steroid anti-inflammatory drugs (NSAIDs) can be used in very limited forms of RP like episcleritis (eye drops) or episodes of arthritis or ear/nose chondritis of minor severity. Colchicine [7] and dapsone [44] may be effective in ear/nose chondritis of minor severity. Dapsone requires screening for glucose-6-phosphate dehydrogenase deficiency before initiating therapy and monitoring for methemoglobinemia [45].

Conventional DMARDs (cDMARDs) are indicated in cases of cortico-dependency or in severe or life-threatening manifestations; however, there is a scarcity of high-quality evidence to guide in choosing between different agents. The most used cDMARDs are methotrexate, leflunomide, azathioprine, mycophenolate mofetil, and ciclosporin based off experience in other inflammatory or auto-immune diseases. Cyclophosphamide is recommended for severe cases where other less toxic agents have failed.

Biological DMARDs are frequently utilized in case of glucocorticoid dependency or in severe or life-threatening manifestations and might be associated with a reduction of some severe manifestations, notably airway involvement according to some recent series [46]. TNF-antagonists are the most frequently used biologic therapy, with Infliximab being the first-choice therapy due to efficacy in about 50 % of patients; however, treatment is stopped frequently for secondary loss of efficacy due to immunization and for infectious adverse effects [47,48]. TNF blockade with Etanercept also seems to be effective in RP [49].

More recently, tocilizumab, an anti-IL-6 agent, has been reported as effective in patients with severe or refractory manifestations [47,50–52]. According to some case reports, anakinra (an interleukin-1 receptor antagonist) may be effective in some patients [53,54]. Abatacept (a CTLA-4 Ig analog) also

showed efficacy in a case of disease which was refractory to three different TNF-antagonists and anti-IL1 (32). However, this agent should be used with caution as some patients with RP have been reported to have worsening of disease [55]. Rituximab (an anti-CD20 depletant drug) seems less effective, with only partial improvement in two patients amongst nine in a small retrospective study [54,56].

A recent literature review in relapsing polychondritis [57] included data from 117 patients with 250 different treatment lines. Findings suggested that methotrexate had the most robust data with a pooled response rate across studies of 56 % [95 % CI: 37–73]. Among biologic therapies, the most effective were: abatacept (pooled response rate: 72 % [95 % CI: 42–95]), tocilizumab (64 % [95 % CI: 53–74]), TNF-antagonists (infliximab, 59 % [95 % CI: 42–75]), anakinra (47 % [95 % CI: 26–68]) and rituximab (43 % [95 % CI: 20–68]).

Laryngeal, tracheal, or bronchial involvement may be treated with local or interventional therapies including steroid infiltrations, endoprosthesis, tracheostomy, mechanical dilatation of stenosis, tracheal surgical resection, or reconstruction. Patients that require airway manipulation should be monitored closely, with consideration of overnight observation. The authors strongly advise that these patients be treated by highly experienced physicians, as procedural interventions can be associated with severe complications [58,59].

In most cases, RP has a chronic disease course with variable frequency of flares [60–62]. Treatment broadly consists of acute management of flares and background suppressive therapy to reduce flare frequency, reduce flare severity, prevent organ damage, and facilitate lower steroid dosing. Management of flares may include purely symptomatic management, increases in steroids, and/or changes in other immunosuppressive agents.

Research agenda and biomarkers

Lack of more complete understanding of the pathophysiology of RP has limited progress with regards expediting diagnosis and the identification of effective treatments. Considering its heterogeneous phenotype and varied presentation, finding a common pathophysiological link continues to be elusive. However, ongoing research into tissue level histology and biomarkers of RP are providing better insight into the cause and progression of the disease.

Research into potential biomarkers and antigenic triggers for RP are ongoing, and new data continues to emerge. Early on, there was great interest in type II collagen, the most abundant collagen found in the body, as a potential antigenic trigger for the disease. Anti-type II collagen antibodies were investigated in patients with RP and other autoimmune diseases. Foidart et al. assessed 15 patients with a prior diagnosis of RP. Of these patients, 5 tested positive for the presence of anti-type II collagen antibodies. For these patients, the antibodies appeared early in the course of the disease and the antibody titer correlated with disease severity and immune-suppressing treatment. The authors hypothesized that the remaining 10 patients were negative for antibodies because they were already receiving immunosuppressive therapy [63]. Other studies have shown that anti-type II collagen antibodies may be positive, but predominantly early in the disease course [31,64,65]. Additionally, antibodies to other less abundant types of collagens, specifically, type IX and XI, have been identified in patients with RP. Anti-collagen antibodies are not specific to patients with RP and have been identified in patients with rheumatoid arthritis [66], juvenile idiopathic arthritis [67], and chronic gouty arthritis [68].

We do not recommend using anti-collagen II antibodies to diagnose RP.

Investigators also have begun looking into the antigenic potential of the collagen support matrix specifically matrillin-1, also known as collagen matrix protein, as it is highly expressed in tracheal and auricular cartilage and serum cartilage oligomeric matrix proteins (otherwise known as COMPs). Antibodies to matrilin-1 are reported to be associated with respiratory involvement in RP and were noted in 13 % of patients in a Swedish study from 2001. The antibodies, however, were also identified in patients with systemic lupus erythematosus and granulomatosis with polyangiitis (7 and 12 % respectively) [69]. Abnormal COMP levels have been detected in patients with RP. Serum COMP levels have been found to be low during active disease and increase back to normal levels when disease

activity improves. This inverse relationship to disease activity suggests COMP levels may play a role in tissue repair after flares [70]. Interestingly, they have also been shown to be pathogenic in mice, inducing arthritis, and it has been hypothesized that these proteins may play a causative role in joint destruction for patients with rheumatoid arthritis [69,71]. A more recent retrospective study of 21 patients with RP demonstrated that elevated COMP levels may be a helpful biomarker of disease activity [48].

Other potential biomarkers have been considered including urinary type II collagen neuropeptide. This peptide was originally studied as a potential biomarker in osteoarthritis (OA) and rheumatoid arthritis (RA). Kraus et al. found a correlation with urinary type II collagen neo peptide and RP disease activity in one patient. The levels improved during treatment with a TNF inhibitor, etanercept, but increased again when the TNF inhibitor was discontinued, and respiratory symptoms flared. Additionally, levels of urinary type II collagen neo peptides were much higher in patients with RP compared to values associated with OA and RA [72]. However, these data are limited to a few patients and have not been validated.

Lastly, Sato et al. identified elevated levels of soluble triggering receptors (STR) expressed on myeloid cells-1 as a potential biomarker of interest for RP, with elevated STR being associated with active disease [73]. However, like the other markers discussed, abnormal findings were not unique to RP and STR also elevated in patients with SLE and RA indicating a lack of specificity. Although research is ongoing, no biomarker or laboratory test has been validated for the diagnosis of relapsing polychondritis; however, some biomarkers may have utility in evaluating for active disease and response to therapy.

Disease activity: the RPDAI

Unfortunately, there are no consensus agreement on outcome measures in RP, which hampers the development of clinical studies. In 2012, Arnaud et al. developed the Relapsing Polychondritis Disease Activity Index (RPDAI) [74] with the help of a world-wide panel of expert's physicians comprising 27 different items with individual weights. To this date, RPDAI still lacks clinical validation. A recent study by Cao et al. [75] showed a positive correlation between RPDAI and three different inflammation markers (C-reactive protein to albumin ratio, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio) in 170 RP patients.

Damage: the RPDAM

Distinguishing between disease activity and damage is a crucial challenge in daily clinical practice to accurately evaluate disease and this distinction particularly important in RP where symptoms may be related to both active disease and/or prior damage. In 2018, Mertz et al. [76] developed a specific index designed to evaluate damage in RP patients, the Relapsing Polychondritis Damage Index (RPDAM) with the help of an international multicenter panel of experts involved in the care of RP patients. The RPDAM included a total of 17 items referring to disease-specific damage (such as ear nose and throat, eye, respiratory, cardiovascular, and associated hematological manifestations) as well as to treatment-related specific damage items. To date, RPDAM also lacks formal clinical validation.

Conclusion

In conclusion, RP is a rare and challenging disease due to its varied presentation, clinical phenotypes, and natural history. Early recognition of symptoms and a multidisciplinary approach to care are crucial for improving the quality of life and prognosis for patients with RP. Diagnosis is clinical and is often delayed due to overlap of symptoms with other more common diseases. Treatment should be individualized. Ongoing research into the pathophysiology of the disease as well as prospective cohort analyses will provide much-needed data to improve the lives and outcomes of patients with RP.

Practice points

- Relapsing polychondritis goes beyond mere ear inflammation; it's a systemic ailment.
- Patients with adult-onset asthma that doesn't respond to treatment might be initially manifesting isolated airway symptoms of this disease.
- Between 40 and 60 % of those diagnosed with VEXAS also have RP. VEXAS should be a consideration for older patients showing symptoms of chondritis, coupled with macrocytic anemia and low platelet counts.
- The approach to treatment is primarily influenced by the specific clinical manifestations and the disease's intensity.
- Upcoming research might focus on identifying unique clinical indicators, which could pave the way for studies aimed at uncovering the disease's molecular origins.

Declaration of competing interest

None.

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