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Review

Relapsing polychondritis: a clinical review for rheumatologists

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Abstract

Relapsing polychondritis (RPC) is a rare autoimmune rheumatic disorder that is traditionally classified as a systemic vasculitis. It is characterized by inflammation of cartilage, and typical presenting features include chondritis of the nasal bridge, auricular chondritis, ocular inflammation and involvement of the bronchial tree. Its rarity often leads to considerable delay in establishing a diagnosis and poses a significant management challenge to clinicians, as no conventional guidelines exist. This review summarizes the clinical features of RPC and provides guidance for rheumatologists on making the diagnosis and assessing organ involvement. The current state of RPC management is reviewed, with a focus on the use of the anti-TNF-α agents in patients with pulmonary involvement, the leading cause of mortality and morbidity in RPC.

Key words: relapsing polychondritis, relapsing polychondritis disease activity index, pulmonary involvement, DMARD, biologic therapy

REVIEW

Rheumatology key messages

- Relapsing polychondritis is a rare, destructive autoimmune disorder of cartilage.
- Laryngotracheobronchial involvement is common in relapsing polychondritis, representing a significant proportion of associated morbidity and mortality.
- Case reports support TNF-α antagonist use, particularly infliximab, in the management of pulmonary relapsing polychondritis.

Introduction

Relapsing polychondritis (RPC) is a rare, episodic (relapsing–remitting), progressive inflammatory disorder involving immune-mediated destruction of cartilaginous structures; predominantly the ears, nose, joints and respiratory tract. The aetiology of RPC is unknown, and the pathogenesis appears to be mediated by an autoimmune reaction to type II collagen, which is abundant in cartilage and the sclera [1, 2].

RPC affects 1 in 1.4 million people per year in the UK, with a standardized mortality ratio of 2.16 [3]. Onset may be sudden, although in mild cases it can be insidious. Peak incidence is in the fifth decade of life (40–55 years old), but the disease has been described in young children and the very elderly. The majority of the reported cases in the literature are of white Caucasian decent, but all ethnic groups are susceptible.

The diverse and non-specific clinical features of RPC alongside its relative rarity frequently leads to diagnostic delay [3]. RPC patients may develop significant disabilities during the disease course, including impairments in hearing and vision, and 30–50% suffer pulmonary complications [1, 4–6]. RPC patients with significant respiratory tract involvement have a poor prognosis, and mortality is most commonly attributable to laryngotracheobronchial disease, infections or cardiovascular complications [3].

Organs involved in RPC

Ears

Auricular chondritis is the most common clinical manifestation and is often the main presenting feature [7, 8]. It leads to erythematous inflammation and swelling of the external ear, with sparing of the lobule. Repeated episodes of chondritis may lead to permanent damage, such as cauliflower ear, extensive calcification or limp pinna (the forward listening ear). Furthermore, thinning of the cartilage makes underlying vasculature more visible (the blue ear sign) [6, 9–12]. Less common manifestations

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include sensorineural hearing loss and tinnitus [7, 8, 13]. This hearing loss is a separate entity from the conductive hearing loss that may be experienced because of inflammation of the external auditory meatus [9].

Eyes

Ocular manifestations of RPC are also common and, if not present at onset, are likely to develop during the course of the disease. The most common ocular presentation is scleritis, usually anterior, or episcleritis. Conjunctivitis is also relatively common. RPC eye disease is accompanied by generalized inflammation, hence proptosis and lid oedema may be seen. Keratitis and uveitis have been reported to a lesser degree. More severe ocular manifestations, including retinal artery and vein occlusion, optic neuritis, retinopathy and retinal detachment, have all been reported but are rare [2, 9, 14, 15].

Nose

Nasal chondritis is less common than auricular chondritis but follows a similar course and can be the presenting complaint. It is characterized by painful inflammation of the nasal cartilage and can often cause the nose to feel blocked [8, 9]. RPC can lead to permanent damage in the form of a saddle-nose deformity [13]. Epistaxis, rhinorrhoea and crusting of the nose also feature [6].

Joints

Costochondritis is commonly reported in RPC patients as retrosternal chest pain and, if severe, can impair breathing. It is rarely an isolated presenting feature, but develops in a sizeable proportion of patients [16].

Joint problems are the second most common manifestation of RPC. Patients generally complain of arthralgia, and this is a common reason for presentation. Peripheral joint disease in RPC is asymmetrical and intermittent and affects both small and large joints, with axial sparing. It is usually a non-destructive, non-erosive, seronegative inflammatory oligo/polyarthritis. Tenosynovitis has been reported, albeit sparingly [9, 13].

Cardiovascular system

Cardiovascular involvement is the second most common cause of death in RPC after respiratory causes. The most common cardiovascular manifestation is aortic regurgitation attributable to aortic root dilatation. Mitral regurgitation is also seen, but to a much lesser degree, and its aetiology is more heterogeneous. Sinus tachycardia is often seen, and varying degrees of atrioventricular block have also been reported. Rarer cardiac problems include pericarditis and myocarditis. The most common vascular complication is aneurysmal disease, predominantly in the ascending thoracic aorta, accompanied by aortic regurgitation. Although aortic disease is by far the most common vascular complication, extra-aortic sites of aneurysms, such as cerebral or iliac arteries, have been reported. Other vascular problems include vasculitis and thrombophlebitis. Owing to the insidious nature of these vascular problems, regular follow-up and monitoring are justified in RPC patients [4, 9, 13, 16–19].

Skin

Non-specific dermatological manifestations, such as purpura, papules and nodules, are common in RPC [13], as are aphthous ulcers and distal skin ulceration, the latter thought to be attributable to local vasculitis. The presence of oral and genital ulcers plus other Bechet's-like phenomena, alongside RPC, is referred to as mouth and genital ulcers with inflamed cartilage (MAGIC) syndrome [20]. Recently, a distinct annular-shaped, eruptive urticaria, distributed on the upper trunk and shoulders, which typically precedes chondritis, has been suggested to be specific to RPC. It also appears to be a marker of patients with myelodysplastic syndrome, a disease commonly associated with RPC [8].

CNS

Neurological involvement is rare; however, it confers a high morbidity and mortality. The most common neurological manifestations are palsies of the fifth and seventh cranial nerves [16]. Meningitis, encephalitis, stroke and aneurysms have also been described in RPC [9, 21]. An increasing volume of anecdotal evidence may implicate RPC as a very rare cause of dementia [21–24].

Renal

Renal involvement is rare; however, if it is present it indicates a poorer prognosis [16]. The most common finding is mesangial proliferation, followed by segmental necrotizing glomerulonephritis. IgA nephropathy and tubulointerstitial nephritis have also been reported [9, 13, 16, 25].

Gastrointestinal involvement

The prevalence of gastrointestinal involvement is still unclear, but there have been reports of concomitant IBD and autonomic dysfunction [13].

Laryngotracheal and pulmonary RPC

Up to half of patients with RPC will develop respiratory problems during the course of the disease, and in half of these patients airway symptoms are the presenting feature. Respiratory complications and lower respiratory tract infections are the most common causes of death in RPC [4, 6]. Laryngeal chondritis occurs in more than half of patients and may present with hoarseness, tenderness of the tracheal rings, cough, breathlessness and stridor. Localized subglottic stenosis like that seen in granulomatosis with polyangiitis is unusual. Respiratory symptoms are typically attributable to inflammation, leading to airway narrowing or loss of cartilaginous structural support. The radiological sequelae of pulmonary RPC are anterior airway wall thickening, airway stenosis either localized or diffuse, depending on disease severity, and tracheobronchomalacia [26]. The latter, attributable to the loss of cartilaginous integrity, results in dynamic airway collapse, especially during forced expiration, and can often be identified on pulmonary function tests and dynamic CT

studies [26]. Chronic laryngotracheal and bronchial chondritis can cause life-threatening airway narrowing and represents advanced disease and a poor prognosis. The classical pathophysiology of airways disease in RPC is depicted in Fig. 1.

Diagnosis and investigations

Diagnosis is usually clinical, based on McAdam's criteria (Table 1); however, cartilage biopsy sometimes has utility in cases of diagnostic uncertainty. Histology shows fragmented cartilaginous tissue surrounded by fibrous connective tissue with mononuclear inflammatory infiltrates, and fibrosis with areas of perichondral inflammatory reaction.

Initial clinical evaluation of patients with suspected RPC should include ESR and CRP, which are commonly used as surrogates in assessing disease activity and treatment response. The relapsing polychondritis disease activity index has been developed and validated for assessing disease activity and provides a means to quantify disease severity and aid treatment decisions [27]. ANCA screen, urine analysis and renal function help to distinguish RPC from granulomatosis with polyangiitis, a vasculitis which shares many clinical features with RPC. Initial clinical assessment should also include audiometry, an ophthalmology examination and cardiovascular investigations, such as an ECG and/or echocardiogram. Cardiac MRI or CT may also be useful.

Pulmonary function tests are an important tool in the assessment of airway function at presentation and at intervals throughout the disease course, especially if new respiratory symptoms arise. In RPC, an obstructive picture is often seen (Fig. 2). This functional impairment occurs early on in the disease progression, often preceding respiratory symptoms [26].

Patients with suspected airway disease, respiratory symptoms or nasal chondritis (which is associated with an increased risk of airway involvement) require a more thorough evaluation of their pulmonary involvement. Functional and anatomical assessment of their upper and lower airways is essential, with spirometry and chest radiographs supplemented with chest CT. This should be a dynamic CT chest, because expiratory CT abnormalities are a much more sensitive marker of pulmonary RPC than inspiratory abnormalities [28]. Failure to carry out a dynamic study could lead to a higher false-negative rate and unnecessary delay in diagnosis and treatment.

Table 1 The six clinical features of the conventionally accepted McAdam's criteria

McAdam's criteria: three or more of the following features are required for diagnosis
Bilateral auricular chondritis
Non-erosive seronegative inflammatory polyarthritis
Nasal chondritis
Ocular inflammation
Respiratory tract chondritis
Audiovestibular damage

Data taken from [4].

Fig. 1 Diagram showing the mechanisms underlying airway obstruction in relapsing polychondritis

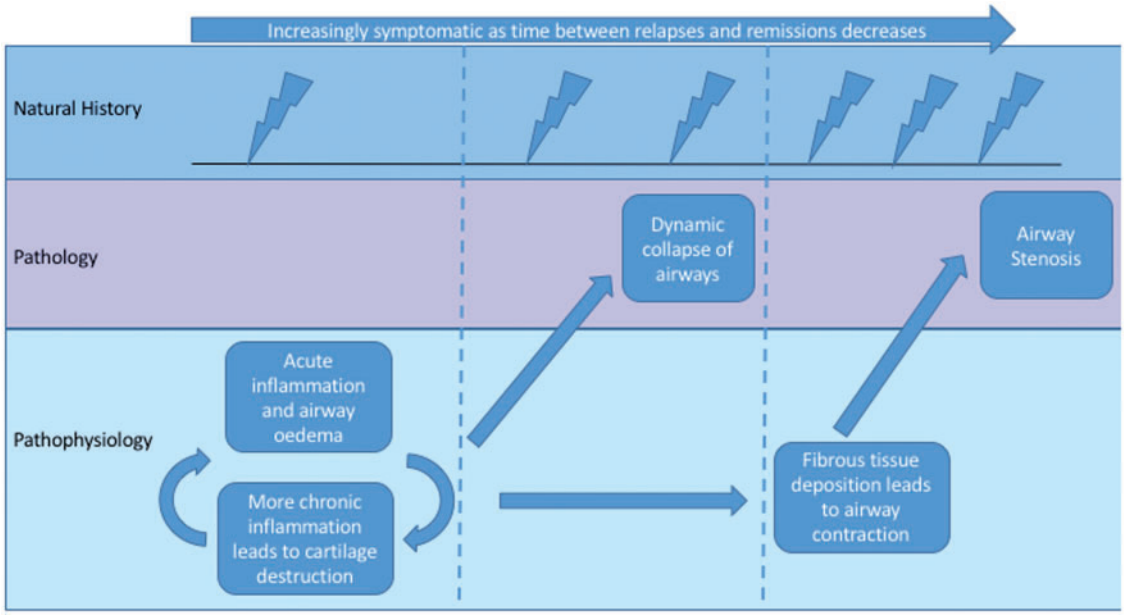
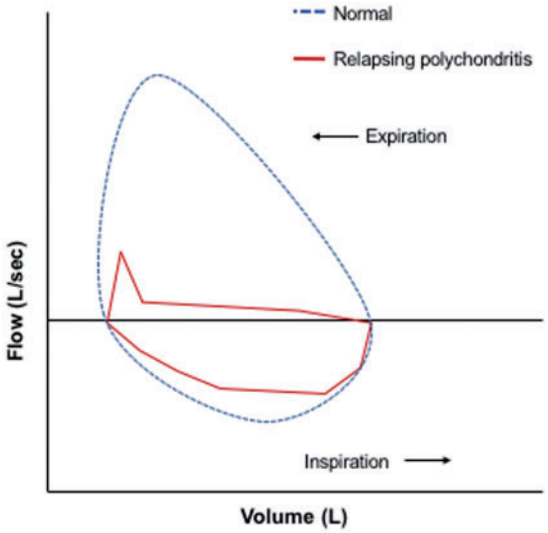


Fig. 2 Schematic flow-loop diagram of relapsing polychondritis patient with severe outflow obstruction



Other imaging modalities may also be useful in RPC. MRI is particularly useful for evaluating the extent of tracheal and laryngeal involvement with its ability to distinguish chronic fibrosis/inflammation from acute oedema and inflammation. Positron emission tomography/CT has also been proposed to have utility in the staging of disease extent and has been shown to detect asymptomatic cartilaginous involvement. Furthermore, it may have greater sensitivity to early treatment responses in tracheobronchial lesions, not seen on CT.

Standard or endobronchial ultrasound bronchoscopy can be used to assess the level of mucosal inflammation (a marker of disease activity) and potential airway collapse. However, this procedure is associated with increased risks of morbidity and mortality owing to the potential anaesthetic and procedural complications; therefore, the decision to carry out bronchoscopy should not be taken lightly and should ideally be performed with airway expertise on hand [26].

Treatment

There is little guidance on the best practice for the management of RPC. Treatment is primarily symptomatic, and no standard therapeutic protocol has been established. Owing to the relative rarity of RPC, there have been no randomised controlled trials to inform clinical practice. Hence, medical therapy has not been standardized and is derived from case-based empirical evidence and expert opinion. The main aim of treatment is to achieve symptom control and maintain airway patency and stability.

The initial management of patients consists of NSAIDs, CSs and/or immunosuppressive therapies. Treatment may relieve the immediate symptoms of RPC, but long-term therapy does not usually prevent disease progression; prognosis is usually poor in patients with severe disease, despite treatment [2].

New approaches have been used, such as TNF-α blockers in the management of severe or treatment-resistant patients, with varying degrees of success. Such biologics have the added potential to slow or even halt the progressive nature of RPC.

Pharmacological management

Treatment is empirically tailored in a step-wise manner (Fig. 3) to the individual patient according to their disease severity. In less severe patients, NSAIDs, dapsone and colchicine have been used. In more severely affected patients, systemic immunosuppression with CSs (oral prednisolone) is required. Cytotoxic agents (MTX, AZA, ciclosporin and chlorambucil) have also been used as steroid-sparing alternatives.

Biologics in RPC

With the advent of mAb therapies, new therapeutic horizons arose for RPC. With the mainstay of previous treatments focused on symptomatic relief and limiting disease activity, biologics facilitated the potential to influence upstream factors in the destructive inflammatory cascade. Biologics thus offer the hope of attenuating or perhaps halting the progression of RPC. A number of biologics have been used in RPC, including: anti-TNF-α (infliximab, etanercept, adalimumab), anti-IL6 (tocilizumab), anti-CD20 (rituximab), anti-IL1 (anakinra) agents and T-cell co-stimulatory/activation inhibitors (abatacept). However, these are all case reports or small case series, and there are no controlled trials of these agents.

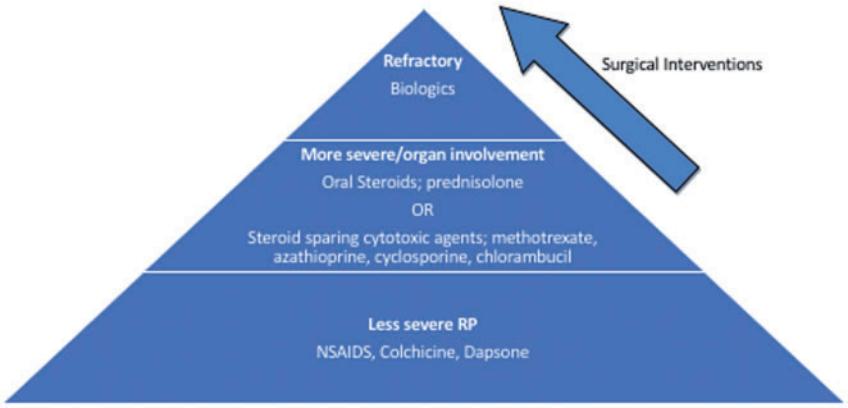
Anti-TNF-α agents

RPC bears many of the hallmarks of a TNF-α-mediated disease; type II collagen-sensitive T-cell clones have been identified in RPC, suggesting a Th1 phenotype autoimmune response, causing a pro-inflammatory, TNF-α-driven cascade. TNF-α has also been demonstrated *in vitro* to induce the synthesis and release of matrix-degrading proteinases from chondrocytes, of the type that causes damage in RPC [29, 30].

Some case reports and small case series have reported the efficacy of anti-TNF-α agents in patients refractory to other anti-inflammatory or immunosuppressive drugs. The successful treatment of patients with infliximab, etanercept and adalimumab has been reported [13, 31–38]. Anti-TNF-α agents may have a role earlier in the disease course as CS-sparing agents. Infliximab may be considered a second-line therapy for RPC, in conjunction with MTX, switching to another biologic (tocilizumab or abatacept) in cases of loss of efficacy of infliximab as third-line therapy.

Infliximab has been trialled in a variety of presentations of RPC, from mild ear and nose chondritis to severe pulmonary inflammation. A recent meta-analysis of cases reporting the use of anti-TNF-α agents in RPC found 43 cases of their use, 31 of these cases used infliximab. Eighteen of the 31 patients responded positively to infliximab, and of the 13 who did not respond to infliximab, 4

FIG. 3 The empirically tailored, step-wise approach to current relapsing polychondritis treatment



did not respond to another anti-TNF agent (etanercept or adalimumab) [39]. Removing these anti-TNF-resistant patients, 18 of 27 anti-TNF-sensitive patients responded well to infliximab.

Infliximab in RPC with pulmonary involvement

Infliximab is a chimeric antibody, with a murine F_{ab} region attached to a human F_c domain. The murine part of the antibody is immunogenic in humans, which accounts for the allergic-type side-effects reported, as well as the loss of efficacy over time. The dose used is generally that used in the treatment of RA and is usually well tolerated. However, a number of adverse effects, some severe, have been reported in cases of RPC. A total of seven drug-related adverse events have been reported in the literature; these include injection-site reactions, cellulitis, sinusitis, otitis, herpes zoster reactivation and pneumonia [31].

Interestingly, of the reported cases on the use of infliximab, RPC patients with pulmonary involvement appear to be over-represented in the respondercases, suggesting they respond selectively better to infliximab, eluding to its potential role in the management of such patients. However, publication bias always needs to be considered when evaluating these reports.

The potential efficacy of such biologics has been shown in RPC-associated laryngotracheal disease. Table 2 summarizes all the reports of the use of infliximab in cases of RPC with pulmonary involvement reported to date.

Of the reports of RPC patients with pulmonary involvement, the majority (86%) responded positively to infliximab, with reduced active disease and CRP/ESR levels [30–34, 40–46]. On average, in RPC patients with pulmonary involvement and reported pre- and post-treatment CRP levels, infliximab was associated with a 50% reduction in CRP levels. In the currently available case reports, infliximab has reportedly led to rapid improvement of several signs, including auricular chondritis [31–35, 42, 47, 48], nasal chondritis [31, 32, 34, 35, 47], laryngotracheal chondritis [31, 34, 43, 48], tracheal thickening [31], dysphonia [31, 32], dyspnoea [31, 33, 34, 42, 43, 48] and obstructive respiratory impairment [31]. The efficacy of infliximab appears to last between 9 months and 3 years, with a persistent decrease of inflammatory markers (ESR/CRP) and steroid-sparing effects.

TABLE 2 Case reports on the use of infliximab in relapsing polychondritis with pulmonary involvement

References	Date	Efficacy
Moulis *et al.* [40]	2013	Responded
Abdwani *et al.* [41]	2012	Responded
Wallace and Stone [30]	2013	Responded
Mpofu *et al.* [31]	2003	Responded
De Barros *et al.* [42]	2010	Responded
Marie *et al.* [32]	2009	Responded
Cazabon *et al.* [43]	2005	Responded
Buonuomo *et al.* [44]	2010	Failed
Subrahmanyam *et al.* [45]	2008	Failed
Kawai *et al.* [46]	2009	Partial response
Ratzinger *et al.* [34]	2009	Responded
Ratzinger *et al.* [34]	2009	Responded
Richez *et al.* [33]	2004	Responded
Ghosn *et al.* [48]	2008	Responded
Saadoun[a] *et al.* [35]	2003	Responded
Saadoun[a] *et al.* [35]	2003	Responded
Bell[a] *et al.* [47]	2007	Responded

[a]Case of nasal chondritis (associated with early pulmonary involvement) but not explicitly defined as having pulmonary disease.

The reported inconsistent response to infliximab among patients with RPC highlights the need for proper patient selection, and work is required to identify which subsets of patients are most likely to benefit from anti-TNF therapies. The evidence presented here tends to support the use of infliximab in individuals with signs or symptoms of pulmonary involvement. There are also reports of good infliximab response in a patient with significant CNS disease [49]. CNS involvement tends to indicate severe RPC, in a similar manner to pulmonary involvement, so the

positive response supports the notion of infliximab in refractory cases with organ involvement. However, further work must be done to confirm these observations to clarify the clinical phenotype most suitable for infliximab therapy.

Non-pharmacological management

Non-pharmacological treatment of RPC is primarily focused on the management of airway lesions. Generally, surgery plays a palliative role in RPC, with little curative potential. Procedures such as endoscopic stenting, balloon airway dilatation, tracheostomy, endobronchial laser therapy and laryngotracheal reconstruction can improve quality of life. Such interventions are usually limited to patients who have failed medical therapy, require bridging while initiating medical therapy or have signs associated with increased morbidity and mortality, such as central airway obstruction, severe diffuse or focal stenosis. Plastic surgery can improve overall quality of life by correcting aesthetically unpleasing cartilage deformities [47, 50, 51]. It may also significantly improve ventilation in patients with advanced upper respiratory tract RPC [52].

Non-invasive ventilation and continuous positive airway pressure may be effective for the prevention of expiratory airway obstruction and associated respiratory symptoms. This should be considered alongside medical therapy, especially in elderly patients with respiratory tract involvement [53] or patients with tracheobronchomalacia [54].

Haematopoietic stem cell transplantation and myeloablation have been used in patients with severe organ-threatening RPC [55, 56]. These have the benefit of countering not only the purported autoimmune component of the pathophysiology of RPC, but also the myelodysplastic syndromes that are frequently associated with RPC [8, 57].

Summary

RPC presents clinicians with a challenging therapeutic conundrum, with few guidelines on the best practice in the use of biologics in treatment-resistant cases. TNF-α antagonists appear to be effective in the management of RPC and could be considered as second-line CS-sparing agents, after considering their risk–benefit ratio.

The current data from case reports support the use of infliximab in RPC with pulmonary involvement, with early therapy being associated with improved outcomes. Interestingly, there were a number of patients who responded favourably to infliximab who were not known to have pulmonary involvement (i.e. had not undergone testing to display this) but had features associated with early pulmonary involvement (e.g. significant nasal chondritis) [35, 47]. This might support the timely use of infliximab in such patients. More work is required to elucidate the start and end points of this therapeutic window. Certainly, early detection of pulmonary involvement is key to reducing morbidity, but potentially also to the selection of patients to commence infliximab therapy. Ultimately, the early use of infliximab in patients with clinical suspicion of early pulmonary involvement may delay or even prevent the appearance of debilitating pulmonary symptoms. Hence, we recommend a robust respiratory surveillance plan alongside cardiovascular surveillance in all patients with early or associated pulmonary features, and the aggressive treatment of those with pulmonary pathology, in order to retard potential deterioration.

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