Relapsing polychondritis
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Abstract
Relapsing polychondritis (RPC) is a unique and rarely observed autoimmune condition regarded as recurrent extensive chondritis of the auricular, nasal, and tracheal cartilages. Moreover, heart, main arteries, skin, and eyes may be involved. Several forms of clinical manifestations may be seen, and the pathogenesis still remains anonymous. A concomitant disease, particularly myelodysplasia or other systemic autoimmune disease can be detected in one-third of the patients with RPC. The treatment of RPC should be considered on personal basis and classified according to disease activity and severity. This study reviews the available data on clinical manifestations, pathogenesis, diagnosis, and therapeutics of the RPC.

Keywords: Relapsing polychondritis, clinics, review

Relapsing polychondritis
Relapsing polychondritis (RPC) is an autoimmune disease characterized by the inflammation of cartilaginous tissues. The disease can affect several organs, including proteoglycan rich tissues, particularly ears, nose, respiratory tract, eyes, and joints (1-3). Owing to the widespread diversity of clinical manifestations and rarity of the disease, diagnosing it in the early stages may be challenging. Approximately 30% of the patients with RPC appear to have an association with a different disease, frequently several forms of autoimmune rheumatologic disease or myelodysplastic syndrome (MDS) (3). This review reveals clinical manifestations, pathogenesis, diagnosis, and treatment of the rare RPC disease.

Epidemiology and genetics
The incidence and prevalence of RPC are not exactly known. RPC is seen more common in Caucasians, and a recently study reported that the calculated prevalence is 4.5 cases/million in defense population (4). Although RPC can occur at all age groups, the starting age of the disease is the fifth decade of life. Generally, studies (5, 6) showed no significant gender predilection, but Trentham et al. (7) found a slightly female predominance. Although the studies indicate a possible genetic contribution, RPC is still regarded as a nonfamilial disease.

Genetic studies have identified a relationship only between RPC and human leucocyte antigen (HLA)-DR4. A recent study (8) investigated the frequency of HLA-DR4 in patients with RPC and it was found to be up to 56% in the patient group and 26% in the healthy control group. On the contrary, in case of rheumatoid arthritis, a definite relationship between specific DR4 subtype alleles and RPC was not identified. Similarly, an important link was found between HLA-DR6 positivity and clinical findings of RPC, but the significance of this result is not clearly understood (8).

Etiopathogenesis
The etiopathogenesis of RPC is still anonymous. Nonetheless, it seems to be a combination of constituents comprising genetic predisposition, a triggering factor, and presence of autoimmunity.

The triggering factors can be chemical, toxic, and infectious agents or direct trauma. Recently, RPC cases have been reported (9) after a trauma of the pinna and (10) intravenous administration of an indefinite substance that may have a direct toxic effect on the cartilage. This suggests that there may be a direct association with trauma and the triggering of autoimmune phenomena. Cañas et al. (11) conducted a study in patients with RPC and showed that patients who had previous cartilage trauma had more autoimmunity features than those who did not have trauma. Possible mechanisms include that cryptogenic antigen release, recognition of pathogenic structure, and metabolic changes generated by trauma (12).

The propensity of RPC to involve cartilaginous structures proposes the occurrence of humoral immunity against this proteoglycan rich tissue. Using the indirect immune fluorescence method, circulating and tis-
the activation of T cells lead to the production of helper T cells 1 (Th1) cytokines containing tu-
more necrosis factor alpha, interferon-γ, interleu-
kin-8, and macrophage inflammatory protein 1 
in RPC cases (21, 22). It can be hypothesized that 
a damage to the cartilage containing chondro-
cyte epitopes leads to cytokine release and local 
inflammation following autoantibody produc-
tion in an inherently susceptible host (22).

Clinical features
The clinical picture of the RPC changes with 
severity and duration of the disease. The most 
common and characteristic feature is auricular 
involvement, but other sites of the body and 
tissues may be involved.

Auricular involvement is present in 90% of 
the patients with RPC, and inflammation is restrict-
et to the cartilaginous fragment of the auricle. 
Earlobes are typically protected from inflamma-
tion. (Figure 1). Most patients refer to medical 
attention with auricular discoloration, tender-
ness, or pain (23, 24). Attacks frequently occur 
in a relapsing–remitting pattern and may cause 
deforments of the pinna. In conjunction with 
common symptoms, there may be infrequent-
ly seen findings in approximately one-third of 
the patients with RPC with ear involvement. For 
instance, inner ear inflammation may cause im-
paired hearing, tinnitus, and vertigo (25).

Ocular inflammation in RPC can affect any part 
of the eye and may affect 20%–60% of the RPC 
cases. Most common ocular manifestations 
are episcleritis, peripheral ulcerative keratitis, 
scleritis, and uveitis (24, 26).

Respiratory tract manifestations of active RPC 
include coughing, roughness, aphonia, wheez-
ing, dyspnea, or sensitivity above the trachea 
(5, 28). Approximately 50% of the patients with 
RPC complicated by laryngo-tracheobronchial 
disease, which may lead to airway obstruction 
resulting in even death. Tracheostomy or a 
stent implantation may be compulsory in se-
vere obstructions (29).

Arthritis is the first presenting symptom in 33% 
of the patients with RPC and is eventually ob-
served in 50%–75% of the patients with RPC 
(30). RPC characteristically affects the manu-
brioisternal, sternoclavicular, and costochon-
dral joints. Any joint may be involved, but the 
frequently affected joints are the metacarpo-
phalangeal, proximal interphalangeal, knees, 
and wrist joints. Usually, arthritis is seen as 
polyarthritis or oligoarthritis with or without 
synovitis and may last from weeks to months. 
It has an episodic, self-remitting, asymmetric, 
nonerosive, and nondeforming course (31).

Approximately 10% of the patients with RPC 
have clinically remarkable valvular disease most-
ly affecting aortic or mitral valves. Additionally, 
cardiac involvement may be associated with 
pericarditis, heart blocks, and myocardial infar-
ction. Valvular involvement can occur any time 
during the disease course (32). Progression of 
the disease is often insidious; as a result, echo-
cardiography should be periodically performed 
to determine valvular dysfunction (33).

Renal disease arises in a minority of RPC cas-
es. Various kidney pathologies can occur in 
RPC cases, including immunoglobulin (Ig) A 
nephropathy, tubulointerstitial nephritis, and 
glomerulonephritis (27, 34).

In addition to audiovestibular manifestations, 
nervological involvement in RPC appears in 
approximately 3% of the cases. The most common 
nervological features are cranial neuropa-
thies of the second, sixth, seventh, and eighth 
nerves. However, miscellaneous nervological 
conditions can occur such as hemiplegia, sei-
zures, organic brain syndrome, dementia, and 
cerebral dysfunction (3, 35).

Several nonspecific skin lesions may develop in 
patients with RPC. Almost 36% of the patients

<table>
<thead>
<tr>
<th>Disease Group</th>
<th>Subtype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Connective tissue diseases</td>
<td>Systemic lupus erythematosus, Sjögren’s syndrome, systemic sclerosis, rheumatoid arthritis, juvenile idiopathic arthritis</td>
</tr>
<tr>
<td>Spondyloarthritis</td>
<td>Ankylosing spondylitis, reactive arthritis, psoriatic arthritis</td>
</tr>
<tr>
<td>Systemic vasculitis</td>
<td>ANCA-associated vasculitis, Takayasu arteritis, Behçet’s disease, polyarteritis nodosa, cryoglobulinemia</td>
</tr>
<tr>
<td>Hematologic diseases</td>
<td>Myelodysplastic syndrome, lymphoma</td>
</tr>
<tr>
<td>Gastrointestinal diseases</td>
<td>Inflammatory bowel disease, primary biliary cirrhosis</td>
</tr>
<tr>
<td>Dermatologic disease</td>
<td>Sweet syndrome, dermatitis herpetiformis, lichen planus, psoriasis</td>
</tr>
<tr>
<td>Other inflammatory disease</td>
<td>Retroperitoneal fibrosis, meningoencephalitis, familial Mediterranean fever, sarcoidosis, autoimmune thyroid disease</td>
</tr>
</tbody>
</table>

*Adopted from reference 28
ANCA: anti-neutrophilic cytoplasmic antibody

Figure 1. Auricular involvement characterized by redness, swelling of the pinna, and sparing of the lobule.
have skin lesions such as oral or skin ulcers, papules, purpura, and nodules. Skin biopsy studies show nonspecific findings, including cutaneous leucocytoclastic vasculitis, small vessel thrombosis, and panniculitis (33, 36).

**Associated diseases**

As many as one-third of the patients with RPC have a concomitant disease including systemic vasculitis, dermatologic or hematologic disease, or other systemic rheumatic disease (Table 1) (3, 28, 36). An intercurrent disease may precede RPC, occur after the diagnosis of RPC, or present simultaneously with RPC. In the last setting, RPC symptoms and signs may be the cause for hospital admission.

**Diagnosis**

Relapsing polychondritis has no pathognomonic clinical, radiological, and histopathological features. The diagnosis is established by the constellation of clinical manifestations, complementary laboratory data, radiological procedures, and biopsy of a cartilaginous site.

Well-known diagnostic criteria are the original “so-called” McAdam’s criteria, which needs the existence of three or more of the clinical findings summarized in Table 2 for diagnoses (5). Damiani et al. (37) suggested a new set of criteria including histological features and therapeutic responses (Table 2).

**Table 2. Criteria for diagnosing relapsing polychondritis* (5, 37)**

<table>
<thead>
<tr>
<th>Author</th>
<th>Criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>McAdam et al.</td>
<td>Recurrent chondritis of both auricles</td>
</tr>
<tr>
<td></td>
<td>Nonerosive inflammatory polyarthritis</td>
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<tr>
<td></td>
<td>Chondritis of nasal cartilages</td>
</tr>
<tr>
<td></td>
<td>Inflammation of ocular structures</td>
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<tr>
<td></td>
<td>conjunctivitis/keratitis/scleritis/uveitis</td>
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<tr>
<td></td>
<td>Chondritis of respiratory tract</td>
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<tr>
<td></td>
<td>laryngeal/tracheal cartilages</td>
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<tr>
<td></td>
<td>Cochlear and/or vestibular damage</td>
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<tr>
<td></td>
<td>neurosensory hearing loss/tinnitus/vertigo</td>
</tr>
<tr>
<td>McAdam et al. (5)</td>
<td>Requires 3 of 6 criteria to diagnose</td>
</tr>
<tr>
<td>Damiani et al. (37)</td>
<td>3 of 6 McAdam et al. (5) criteria or</td>
</tr>
<tr>
<td></td>
<td>1 of 6 McAdam et al. (5) criteria and a positive histologic confirmation or</td>
</tr>
<tr>
<td></td>
<td>2 of 6 McAdam et al. (5) criteria and a response to corticosteroid or dapsone</td>
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</tbody>
</table>

*Adopted from reference 31.

There is no specific laboratory test for RPC, but measurement of acute phase reactants can be helpful similar to that in other autoimmune diseases. Approximately 10% of the patients may have peripheral eosinophilia that suggests vasculitis as a potential differential diagnosis. Particularly when there is an overlap with other rheumatologic disorders, patients with RPC may have a positive serology such as rheumatoid factor, anti-neutrophil cytoplasmic antibody (ANCA), anti-nuclear antibody (ANA), and false-positive venereal disease research laboratory (VDRL) tests (27, 38, 39).

In addition to the clinical evaluation and laboratory tests, the work-up should include imaging studies such as dynamic expiratory computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and Doppler echocardiography along with lung function tests. When patients are diagnosed with RPC, large airways should be scanned by CT to evaluate laryngo-tracheal bronchial luminal narrowing, wall thickening, and calcification of cartilaginous structures (27, 40). MRI is more advantageous than CT to discriminate among fibrosis, inflammation, and edema (41, 42). PET/CT is used for the early diagnosis of RPC as well as for the assessment of activity and extent of disease (43, 44). Doppler echocardiography is used to evaluate the involvement of cardiac valves.

**Treatment**

There are not many clinical trials to estimate treatment modalities for RPC because of the rarity of the disease. The pharmacological approach is mainly based on large series of single or multiple case reports. Despite successful suppression of the clinical features, no therapy has been proved to change the natural course of the disease.

Medical treatment of RPC depends on disease severity and extension of the disease. Active large airway, cardiac, and main artery involvement usually demonstrate the need for aggressive therapy. Recently, an activity scoring system has been developed for RPC. RPC Disease Activity Index (RPDAI) can be used for the assessment of activity in routine clinical practice.

For patients with nasal, auricular, and articular chondritis but no visceral involvement, anti-inflammatory drugs, colchicine, or dapsone can be attempted with limited efficacy (6, 7, 33). Low-dose glucocorticoid therapy is often required. For patients with large airway, ocular, cardiovascular, neurologic, or renal disease, the initial treatment is determined by the assessment of disease severity. For those with relatively mild involvement, oral glucocorticoids can be initially used. In patients with potentially severe manifestations (severe laryngeal or tracheobronchial chondritis, very recent and abrupt onset of sensorineural hearing loss, or systemic vasculitis with poor prognosis factors), methylprednisolone bolus therapy (15 mg/kg/day) combined with an immunosuppressive or immunomodulatory agent (4, 5, 6, 34) can be beneficial as an initial therapy.

Several immunosuppressive and anti-inflammatory drugs were used to lessen the duration and doses of corticosteroid treatment. The frequently used immunomodulatory drugs are cyclophosphamide, methotrexate, azathioprine, and cyclosporine. Cyclophosphamide is a commonly used immunosuppressive drug based on experiences in other systemic rheumatic diseases, particularly systemic vasculitis (45, 46). It can be used at a quantity of 1–2 mg/kg (Maximum dose 150 mg/day) per oral until a clinical response is obtained. After achieving remission, the dose should be reduced to a maintenance level (46).

The efficacy of biological agents in the treatment of RPC has been recently reviewed (47). This study showed that infliximab has been the most frequently used biological agent so far with variable results that are difficult to interpret. Nearly half of the patients benefited from infliximab therapy but several experienced
infections, of which a few were fatal (47). Rituximab usually has no treatment effect. Abatacept was used in a pilot study of four patients and for exploratory purposes in three patients with variable results (47). Other biological agents attempted in case of RPC include anakinra, tocilizumab, etanercept, adalimumab, and certolizumab, but the numbers of treated patients are too small to draw definitive conclusions (47).

Surgery may be needed in selected patients owing to some of the visceral manifestations such as the segmental collapse of airways (48, 49). Surgical management may also be necessary for intractable heart failure because of valvular regurgitation and for aortic aneurysms.

Prognosis

Improvements in the outcomes of patients with RPC have been achieved in recent years, probably because of better comprehension of the disease, thereby allowing the diagnosis of mild forms and development of better treatment strategies. Survival rates were reported to be increased from 70% at 5 years (5, 6) to 91% at 10 years in a recent study (33, 50). Main causes of death in patients with RPC are specific organ involvements such as airways, blood vessels, concomitant MDS, and infections in which development is facilitated by the treatment itself (5, 6). Despite the course of RPC being rapidly lethal, the more common patterns reproduce a relatively benign disease. Some disabilities can be seen in the chronic phase of RPC, including visual impairment, audiovestibular dysfunction, and cardiopulmonary disease (7, 33, 50).

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4. Mathew SD, Battafarano DF, Morris MJ. Relapsing polychondritis in the Department of De-