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Relapsing polychondritis: a chameleon among orphan diseases

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Summary Relapsing polychondritis (RPC) is a rare disease with recurrent episodes of inflammation of cartilage tissue leading to fibrosis and organ damage. Despite unknown etiology, there is some evidence of a genetic predisposition. The clinical presentation is heterogeneous and an association with other autoimmune disorders such as rheumatoid arthritis or different forms of vasculitis has been described. All organ systems containing cartilage can be affected, such as ear, nose, joints, trachea, aorta, and coronary arteries. Given the broad spectrum of potential manifestations, a variety of medical specialists may be involved in the management of RPC patients. As establishing the diagnosis of RPC may be difficult, an interdisciplinary approach may be preferable. Treatment options include glucocorticoids, dapsone, disease-modifying antirheumatic drugs, and biologics. Prognosis is as heterogeneous as the clinical picture, depending on the severity of organ damage. In this paper we give an overview of the current knowledge with regard to pathogenesis, clinical picture, diagnosis, and therapy of RPC.

Keywords Polychondritis · Cartilage · Inflammation · Nose · Ear

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Rezidivierende Polychondritis: ein Chamäleon unter den seltenen Erkrankungen

Zusammenfassung Die rezidivierende Polychondritis (RPC) ist eine seltene Erkrankung, die zu einer Entzündung von Knorpelgewebe führt. Ihre Ätiologie ist unbekannt. Es gibt jedoch Hinweise auf eine genetische Prädisposition. Die Erkrankung ist assoziiert mit anderen Autoimmunerkrankungen, wie rheumatoider Arthritis oder verschiedenen Formen der Vaskulitis. Das klinische Bild ist sehr vielfältig. Alle Organsysteme mit Knorpelgewebe können betroffen sein, wie Ohren, Nase, Gelenke, Trachea, Aorta und Koronararterien. In Anbetracht des breiten Spektrums möglicher klinischer Manifestationen sind eine Vielzahl unterschiedlicher medizinischer Fachbereiche mit dem Management der RPC konfrontiert. Die Diagnosestellung kann schwierig sein, daher empfiehlt sich die Zusammenarbeit von Spezialisten unterschiedlicher Disziplinen. Die Therapieoptionen reichen von Glukokortikoiden über Dapson, traditionelle Basistherapeutika („disease modifying antirheumatic drugs“, DMARDS) bis zu Biologika. Die Prognose ist ebenso heterogen wie das klinische Bild und in erster Linie abhängig von einer potenziellen Organbeteiligung. In diesem Artikel geben die Autoren einen Überblick über den aktuellen Stand zu Pathogenese, klinischer Präsentation, Diagnose und Therapie der RPC.

Schlüsselwörter Polychondritis · Knorpel · Entzündung · Nase · Ohr

Introduction

Relapsing polychondritis (RPC) can be seen as a prototype orphan disease. It is a systemic inflammatory disorder with unknown etiology affecting mainly car-

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Table 1 Systemic diseases reported to be associated with RPC. (Modified from McAdam et al. [6], Trentham et al. [7])

Systemic vasculitides	ANCA-associated vasculitides Behcet's disease (MAGIC syndrome) Hepatitis C Polyarteritis nodosa
Connective tissue diseases	Systemic lupus erythematodes Sjögren syndrome Scleroderma
Rheumatoid arthritis	Seropositive rheumatoid arthritis Juvenile rheumatoid arthritis
Spondyloarthritis	Ankylosing spondylitis Psoriatic arthritis Reactive arthritis
Hematologic diseases	Myelodysplastic syndromes Lymphoma Pernicious anemia Acute leukemia
Other diseases	Hypothyroidism Hashimoto's thyroiditis Ulcerative colitis Graves' disease Myasthenia gravis Primary biliary cirrhosis Mixed cryoglobulinemia Diabetes mellitus Glomerulonephritis

RPC Relapsing polychondritis, *ANCA* Anti-neutrophil cytoplasmic antibodies, *MAGIC* Mouth and genital ulcers with inflamed cartilage

tilage tissue. Clinical manifestation is very heterogeneous.

Pathogenesis

There is some evidence that RPC has an underlying genetic predisposition. In one study, for example, there was an association with *HLA-DR4* [1], whereas in another study, further genes were found to be associated with RPC (*DQB1*0601*, *DQA1*0103*, and *DQA1*0301* [2]). Furthermore, it is assumed that a number of events finally lead to the manifestation of the disease in predisposed individuals [3]. RPC is associated with a number of other autoimmune conditions (systemic vasculitis, rheumatoid arthritis, systemic lupus erythematodes, Behcet's disease, spondyolarthritis, inflammatory bowel disease, primary biliary cholangitis, retroperitoneal fibrosis, familial Mediterranean fever, etc.; Table 1). Interestingly, there are repeated reports of an association with myelodysplastic syndrome [4, 5]. Given these facts, RPC may represent a syndrome rather than a single defined and uniform disease.

Though not finally proven, a theory for the pathogenesis of RPC has been established: it is believed that a number of immunogenic epitopes are more or less masked in the cartilage. If chemical, traumatic, or infectious insults lead to a loss of integrity of the cartilage, antigens may be modified and, finally, these antigens may interact with the immune system [8]. In case of a genetic predisposition this may lead to a destruction of cartilage by the immune system [9], which in turn may cause a broader insult to the cartilage and release additional immunogenic particles. Consequently, the immune system may show reactions to cartilage in remote areas and structures of the body [10].

The histological picture of RPC changes throughout the course of the disease and is, therefore, dependent on the particular point of time at which a biopsy is taken. In early stages, a heterogeneous inflammatory infiltrate, some deposits of IgG, and complement can be found, as well as proteoglycan depletion of the cartilage. As the inflammation proceeds, islands of cartilage arise, which are surrounded by fibrous tissue. In later stages fibrosis is predominant [11].

Clinical presentation

Diagnosing the disease may be challenging. First of all, as RPC is an orphan disease, the diagnosis may not be considered initially and therefore be missed. In addition, especially early signs of the disease may be very unspecific, thereby generating a broad list of differential diagnoses. Furthermore, a number of different medical disciplines are involved in diagnosing and management of RPC, resulting in different impressions of the same disease. Finally, the published evidence clearly represents the limited scientific knowledge about RPC and it appears that severe cases are overrepresented in the published cohort studies.

RPC is infrequently seen in daily clinical practice. The annual incidence is estimated to be about 3.5 per million. RPC may manifest itself in all age groups, but probably peaks between the fourth and sixth decades of life [12]. As mentioned above, the clinical picture shows a multitude of symptoms, resulting in not even considering RPC as a possible diagnosis in atypical cases. In fact, cartilage can be found throughout the whole body, thereby providing a number of potential targets. In addition, RPC may present itself with rather unspecific constitutional symptoms such as fatigue, fever, or weight loss [12].

The hallmark of the disease is inflammation of the pinna. However, while the external ear is affected in 90% of patients during the course of disease, only 40% of cases show initial involvement of the ear. Of note, the earlobe, which does not contain cartilage, is excluded, while the rest of the ear is red and tender (Fig. 1a). This may lead to the differential diagnoses of an infectious disease [13]. The current inflammation may cause destruction of the pinna. However, spontaneous regression has been reported [14]. It is important to recognize that not only the external ear, but also the inner ear can be affected. This may lead to hearing loss, vertigo, and tinnitus [15].

Ocular involvement is found frequently. In one study of the Mayo clinic including 112 patients, 21 cases initially showed ocular involvement, whereas during the course of disease the number of patients with ocular symptoms increased to 57. The reported

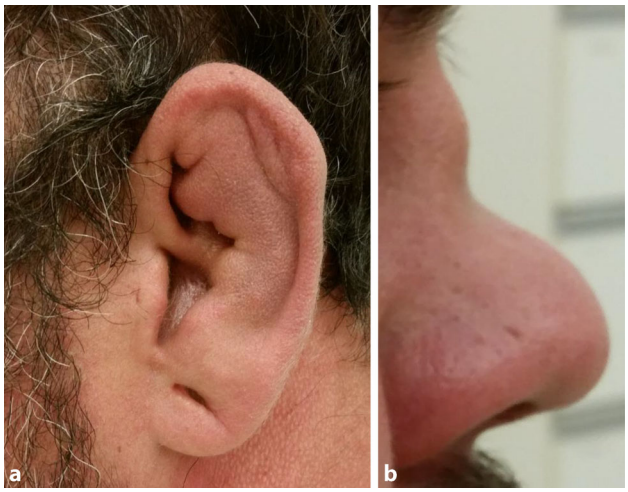

Fig. 1 **a** Relapsing inflammation of the auricular cartilage can lead to irreversible destruction. **b** Saddle nose deformity caused by relapsing polychondritis

manifestations were very heterogeneous (episcleritis, scleritis, iridocyclitis, retinopathy) [16, 17]. Recurrent inflammation of the eyeball may lead to scleromalacia and is associated with the risk of rupture of the eyeball [18].

The upper and lower airways are frequently involved in RPC. Nasal cartilage is affected in 20% of cases and rises up to 60% during the disease course. This may lead to epistaxis and finally to destruction of the nasal cartilage, causing saddle nose deformity (Fig. 1b). Manifestation of RPC in the bronchial tubes may cause severe morbidity. Arriving at the correct diagnosis by examination of the lower airways only may be difficult, especially if typical signs of RPC, such as auricular chondritis or nasal involvement, are missing [19, 20]. Symptoms like hoarseness, cough, or dyspnea may be present, but are very unspecific. Cases of acute airway compromise in patients with RPC have been reported [21]. Bronchoscopy should be avoided or, if necessary, performed with caution, as induction of inflammation through mechanical procedures has been reported [22].

RPC may also lead to arthritis, with frequent involvement of the sternoclavicular, costochondral, and manubriosternal articulations. Also, peripheral arthritis affecting large or small joints, tendovaginitis, and axial spine manifestations have been reported [23].

Additionally, cardiac involvement has been reported, mainly affecting the aortic valve [24]. Other cardiac manifestations of RPC are pericarditis [25], bundle blocks, or coronary arteritis [26]. It must be pointed out that cardiac involvement can progress despite clinical remission [27]. Unfortunately, surgical repair is associated with a high rate of relapse.

Although a number of different renal manifestations have been reported, a disease-specific homogenous pattern does not seem to exist [28]. Furthermore, a variety of manifestations in the central and peripheral nervous systems have been noted (seizures, organic brain syndrome, myelitis, meningitis, dementia, neuropathy) [29–32].

A large spectrum of dermal manifestations, ranging from aphthous ulcers to nodules, purpura, papule, and sterile pustules, as well as phlebitis, ulcerations of the limbs, and necrosis has been described [33]. RPC was repeatedly found to be associated with different forms of vasculitis. The so-called MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) represents a special manifestation of RPC and is regarded as an overlap with Behcet's disease [34, 35].

Table 2 provides a summary of clinical manifestations of RPC at disease onset and during the course of disease.

Diagnosis

There is no specific test to establish the diagnosis of RPC. In fact, a combination of clinical presentation, laboratory parameters, imaging studies, and/or histology may lead to the correct diagnosis of RPC. Published in1976, the McAdams diagnostic criteria have been used to diagnose RPC (Table 3). Since then, the initial criteria have been modified accordingly [6]. Laboratory findings compatible with RPC are prolonged erythrocyte sedimentation rate, elevated C-reactive protein, and anemia. Some patients

Table 2 Clinical manifestations of relapsing polychondritis at disease onset and during the disease course. (Modified from McAdam et al. [6], Michet et al. [36], Trentham et al. [7])

	Disease onset (%)	During disease course (%)
Auricular chondritis	22–91	89–95
Arthritis	23–47	52–85
Vasculitis	0–3	10–12
Aortic or mitral regurgitation	0	6–8
Laryngotracheal symptoms	14–38	48–67
Skin involvement	0–7	28–38
Ocular inflammation	14–24	51–65
Nasal chondritis	13–33	48–72
Saddle nose	0–18	20–29
Reduced hearing	7–9	30–46
Vestibular dysfunction	4–5	13–53

Table 3 McAdam et al. criteria [6] (three of six clinical features necessary for diagnosis)

Bilateral auricular chondritis
Nonerosive seronegative inflammatory polyarthritis
Nasal chondritis
Ocular inflammation
Respiratory tract chondritis
Audiovestibular damage

show eosinophilia, whereas positive antinuclear antibodies usually indicate an underlying associated rheumatic inflammatory disease [4].

In a substantial proportion of patients, anti-type II collagen antibodies were found [8, 37]. Their relevance in the pathogenesis of RPC is unclear. In fact, these antibodies seem to be unspecific, as they can be found in a number of other diseases as well [38]. Some patients test positive for anticytoplasmatic antibodies suggestive of an underlying vasculitis [39].

Pulmonary function tests may help to detect lung involvement. Bronchoscopy may be useful in individual cases. As associated with significant risks, this procedure is not recommended as a routine tool in the assessment of pulmonary involvement in RPC [40]. Computed tomography (CT) is very valuable in diagnosing stenosis, wall thickening, or calcification in the large airways; however, routine CTs in full inspiration may miss a number of cases. Additional CT scans in expiration are recommended, which can demonstrate abnormalities like airway collapse in up to 94% of the cases. The most common findings are air trapping and tracheobronchomalacia [41, 42]. In selected cases, magnetic resonance tomography may be helpful [43]. PET-CT (positron emission tomography-computed tomography) scan may reveal active inflammation [44, 45]. In order not to miss cardiac involvement, an ECG (electrocardiogram) may be used to detect arrhythmias or bundle blocks. Echocardiography is useful to demonstrate insufficiencies of the aortic and mitral valve. In addition, the ascending aorta can be examined to search for aneurysms. Magnetic resonance tomography, transesophageal echocardiography, and CT scan may assist in the evaluation of the aorta [46].

Therapy

Therapy of RPC is more or less empiric. Cohort studies were based on data collected over several decades in tertiary referral centers, beginning 1960. Additionally, a large number of case reports and case series were published. These facts make it somewhat difficult to draw firm conclusions regarding the effectiveness of specific treatment forms. Furthermore, it is not clear whether reportedly effective treatment in patients with severe disease is also appropriate in milder forms of RPC.

In cases involving nose, external ear, or joints only, treatment includes non-steroidal anti-inflammatory drugs (NSAIDs), which are frequently combined with dapsone or glucocorticoids [47]. The dosage of steroids is dependent on the activity of RPC. A starting dose of 30 to 60 mg per day is frequently used, reducing the dose during the course of the disease. In situations where steroids or dapsone are not sufficiently effective, a combination of both drugs can be administered. Alternatively, a disease modifying antirheumatic drug (DMARD) can be started. In some milder cases, colchicine might be an option [48, 49].

In patients with potential organ- or life-threatening manifestations (e. g., larynx, lower respiratory tract, central nervous system, ocular, or cardiac involvement), high-dose steroids (e. g., 60–100 mg per day) are used. In addition, DMARDs are usually started. For example, cyclophosphamide (CYC) was frequently used, either in oral or in parenteral form, even though robust data on its effectiveness are not available [28, 50]. This approach has been extrapolated mainly from experiences gained in the management of vasculitis. Following induction therapy, a switch to less toxic drugs for maintenance therapy should be considered (e. g., azathioprine or methotrexate). Beside CYC, some data on other DMARDs like azathioprine [51], cyclosporine A [52], methotrexate [53], and leflunomide [54] have been published.

In recent years, reports on biologicals became available. It should be mentioned that a number of patients in such reports were previously refractory to traditional DMARDs. Infliximab was reported to be an effective drug in individual RPC patients [55–57]. The same applies to etanercept [58–62]. Of note, single case reports exist describing RPC-like disease as a side effect of treatment with TNF (tumor necrosis factor) inhibitors [63, 64]. Additionally, the interleukin-1 blocker (IL-1 blocker) anakinra was reported to be beneficial in individual cases of refractory RPC [65–67].

Tocilizumab, a humanized monoclonal antibody against the interleukin-6 receptor, was found to be effective in some patients who previously did not respond to a number of different treatment strategies [68, 69]. The same is true for abatacept, a molecule blocking T cell costimulation [70].

Rituximab, a B cell depleting agent, does not appear to be sufficiently effective in patients with RPC. In a small retrospective analysis of 9 patients, 7 patients experienced worsening of the disease. Additionally, no partial or complete remission was observed [71]. In a case series reported by Moulis et al., 9 patients received a total of 22 biologicals [72]. TNF inhibitors were most frequently used as first-line biologic therapy and were associated with partial or complete remission in 85.7%. Loss of efficacy was reported in five cases. Abatacept ($n = 3$) and tocilizumab ($n = 2$) were effective as second-line biologic therapy. Anakinra ($n = 2$) and rituximab ($n = 1$) were not found to control the disease sufficiently. Kemta Lekpa et al. published a literature review on the use of biologicals in RPC [73],

analyzing 30 papers including 62 patients treated with TNF inhibitors (n = 43), rituximab (n = 11), anakinra (n = 5), tocilizumab (n = 2), and abatacept (n = 1). Overall, biologicals were reported to be effective in 27 patients, partially effective in 5 patients, and not effective in 29 patients. Four patients died (2 from sepsis, 1 after aortic aneurysm surgery, and 1 death after accidental dislocation of the tracheostomy device).

Surgery or interventional techniques should be reserved for selected cases. In some patients, bronchial involvement may lead to significant stenosis, where interventional techniques may be beneficial. However, these are challenging and can accelerate the inflammatory process [74]. Cardiac surgery due to valve destruction related to RPC has a poor outcome. In one series, 23.8% of patients had to be re-operated upon within the first 4 years. Postoperatively, 52.6% died of a cardiovascular cause [24].

Prognosis

Regarding long-term outcome, only a few reports are available. Michet et al. found a 5-year survival rate of 74% and a 10-year survival rate of 55% [36]. Most frequently, death was caused by infection, vasculitis, and malignancy. Only 10% of deaths among 112 patients were attributed to airway involvement. A recent paper on survival was published by Sharma et al. [75]: 26 patients showed a median survival of 13.5 years. These heterogeneous results may reflect different patient groups as well as the different periods of time at which data were collected.

Conclusion

RPC is a rare condition, causing remitting inflammation in cartilaginous and proteoglycan-rich structures like ears, nose, and tracheobronchial tree. Clinical presentation is heterogeneous and early signs may be unspecific. Nevertheless, diagnosis of RPC should not be delayed or missed, as this may lead to substantial morbidity. Involvement of inner organs may be life threatening. So far, no evidence-based treatment options for the management of RPC are available. Therapy should be tailored to organ involvement and severity of the disease. For milder cases, treatment regimens include NSAIDS, dapsone, colchicine, and/or corticosteroids. Traditional DMARDs (e. g., azathioprine, cyclosporine A, methotrexate, leflunomide) may be used as steroid-sparing agents, especially in severe cases or when glucocorticoids cannot be tapered or discontinued. In patients with potential organ- or life-threatening manifestations, higher doses of glucocorticoids (e. g., 60–100 mg per day) are used. These severe cases may necessitate the use of cyclosporine A. In general, biologicals seem beneficial for the treatment of RPC. However, rituximab appears inferior to other biological agents. Due to the heterogenic course of the disease, an interdisciplinary approach of a team of specialists is advisable, including rheumatologists, otorhinolaryngologists, pulmonary specialists, cardiologists, and even thoracic surgeons. Regular follow-up of patients is highly recommended.

Conflict of interest S. Schumacher and H. Pieringer declare that they have no competing interests.

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