Review article

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RELAPSING POLYCHONDRITIS: FROM ETIOPATHOGENESIS TO THERAPY

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Relapsing polychondritis (RP) is a rare autoimmune systemic disease of nature, with insufficiently elucidated etiopathogenesis, characterized by a predominantly relapsing-remitting course, involving elastic, hyaline and fibrous cartilage and tissues abundant in proteoglycans. It may lead to anatomical and functional impairments, with a potentially fatal outcome despite treatment. It usually manifests in the form of auricular and nasal chondritis and polyarthritis. Involvement of the laryngotracheobronchial tree, as well as heart valves and aorta, with the onset of secondary infections of primarily lower portions of the respiratory tract, are the most common reasons for the lethal outcome. Involvement of the eye in the form of episcleritis, scleritis etc., involvement of the inner ear in the form of vestibular disorders and sensorineuronal symptoms, as well as central and peripheral nervous system involvement, comprise a probable clinical spectrum of RP. The diagnosis of the disease is usually significantly delayed; for the diagnosis, clinical presentation is essential, while laboratory findings play only a supportive role, and imaging methods (CT, PET-CT, MRI) are important in disease activity assessments. Mild forms of RP should be treated with non-steroidal anti-inflammatory agents and low doses of corticosteroids, while severe forms are treated using higher or, as needed, pulse doses of corticosteroids, and with conventional and biological disease-modifying drugs (DMARDs). More advanced forms of aortic and valvular disease require surgical treatment.

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Introduction

Relapsing polychondritis (RP) represents a rare, systemic immune-mediated disease, characterized by recurrent episodes of inflammation affecting the cartilage and tissues abundant in proteoglycans, with consequential anatomical and functional impairments and a potentially fatal outcome. In addition to the involvement of elastic cartilage in the ear and nose, hyaline cartilage of peripheral joints, axial fibrocartilage, and laryngeal and cartilage of the tracheobronchial tree may be affected as well (1). Since different cartilaginous structures are involved, with different resultant symptomatology, the diagnosis is very often delayed. Auricular and nasal cartilages are the ones most commonly involved, with accompanying polyarteritis (2). Since there is a possibility of involvement of the cartilage in the laryngotracheobronchal tree, and tissues rich in proteoglycans, such as the sclera, heart valves and blood vessels, there is an increased risk of permanent or life-threatening consequences. In 30% of RP patients, this disease is associated with other autoimmune diseases, most commonly with rheumatoid arthritis, but also with myelodysplasia and/or systemic inflammatory conditions (3).

The disease was originally described in 1923 and termed "polychondropathia", while the current term RP was first used by Pearson et al. in 1960, who described it as a recurrent disease in 12 patients. The first diagnostic criteria were presented by McAdam et al. in 1976, and their modification was subsequently performed by Damiani and Levine in 1979, and by Michet et al. in 1986 (4).

Epidemiology

The incidence of the disease has been 3.5 cases per one million people, according to the data for the United States (5). The data reported about the population of the affected in the United

Kingdom has indicated the incidence of 0.71 per one million a year, and the prevalence of 9 per one million, suggesting also a frequently delayed diagnosis and a mortality rate more than twice as high as that in the general population (6).

The disease usually starts between the fourth and fifth decades of life, being slightly more common in women compared to men. It occurs among all ethnicities and races, though being more common in whites. In less than 5% of the cases it may occur in pediatric populations, with similar symptomatology as in adults (7).

Etiopathogenesis

A histopathological finding of involved cartilage typically shows an inflammatory infiltrate which consists of T-lymphocytes (mostly CD4 T-cells), macrophages, plasma cells and immune deposits, limited to the perichondrium initially, and extending subsequently to the cartilage itself (1). In a later phase of the disease, chondrocyte apoptosis and focal calcifications or fibrosis can be seen (2).

The disease pathogenesis has not been fully elucidated. It is thought that the presence of HLA-DR4 antigen is important for the disease onset, and humoral and cellular immunities are implicated as well. In RP patients, cartilage-specific autoimmunity is essential, since the presence of circulating autoantibodies against collagen types II, IX and XI has been demonstrated. Autoantibodies against collagen type II are especially important since this type constitutes 95% of collagen in the cartilage and is present in the sclera as well. These antibodies have been found in one-third of the affected with an active disease form, and their titre is positively correlated with disease severity. In addition to collagen II, significant autoantigens are also matrilin-1 and cartilage oligomeric matrix proteins (COMPs). Matrilin-1 is an intercellular matrix protein of the cartilage, contained in a considerable amount by the tracheal, nasal, auricular and chondro-sternal cartilage, while COMPs are mainly contained in the extracellular matrix of the cartilage, ligaments and tendons. There have been reports indicating a positive correlation between the titre of autoantibodies against matrilin-1 and disease severity, while the results indicating a correlation between the titre of autoantibodies against COMP and disease severity have been controversial (1).

The importance of cellular immunity is reflected in the role of chemokines consistent with the Th-1 profile, such as interferon, interleukin (Il)-2 and IL-12, released during this inflammatory process. With disease progression, there occurs a high expression of proteolytic enzymes in perichondral cells and chondrocytes, with matrix metalloproteinases (MMPs) -3, -8 and -9, elastase and cathepsin K and L being the most significant (2, 8).

Finally, it has been thought that still unknown factors, such as possible infectious agents and/or mechanical and chemical aggression in genetically predisposed individuals can cause protein breakdown, with consequential release of cartilage antigens and creation of autoantibodies. Further, the production of proinflammatory cytokines, recruitment of infiltrating cells and action of proteolytic enzymes released by apoptotic chondrocytes result in cartilage destruction (1, 8). There have been descriptions of RP appearing during pregnancy, after a trauma, piercing, after using glucosamine chondroitin preparations, as well as after the use of an anti-TNF drug in patients with ankylosing spondylitis (2, 8).

It has recently been found that a subgroup of RP patients carry somatic mutations in the gene coding for ubiquitin-activating enzyme 1 (UBA1), which is considered to be the cause of the Vacuoles, E1 enzyme, X-linked, Autoinflammatory, Somatic (VEXAS) syndrome. The patients with VEXAS-RP are mostly middle-aged or older males, with frequent hematological disorders and increased mortality rates (9).

Clinical picture

The clinical spectrum of the disease may vary from occasional inflammatory episodes, leading to non-esthetic structural deformities, to serious progressive multiorgan damage, with cardiopulmonary manifestations being the most serious and life-threatening (such as the collapse of the airways, involvement of the aorta and valvular regurgitation) (1–3). In over 80% of RP patients, the disease manifests in the form of auricular chondritis and polyarthritis. The disease can have an abrupt onset, while in milder cases the onset can be rather insidious. Constitutional symptoms in the form of fever, weight loss, night sweats, exhaustion and lymphadenomegaly are often present.

Involvement of the auricular cartilage manifests in the form of pain, swelling and redness of the auricle, with possible additional involvement of the outer and middle ear. Involvement of the vestibular structures or vasculitis of the branches of the internal auditory artery may produce vestibular or sensorineural symptoms. Nasal cartilages are often involved, with the onset of nasal pain, hoarseness, throat pain, difficulty speaking, and nose deformities such as saddle nose or flat nose tip in later phases of the disease (3).

In almost 50% of patients with RP, there is laryngeal or tracheobronchial involvement, which, if remains unrecognized, may lead to strictures, mucosal edema and collapse of the cartilage, with consequential airway obstruction and lethal outcome even in early disease stages (10, 11). Pain and stiffness of the thyroid cartilage and trachea are also possible, as well as hoarseness, non-productive cough, dyspnea, stridor and

wheezing, and also subglottic inflammation, collapse of the trachea, tracheobronchomalacia or secondary pulmonary infection. Infiltrations in the lungs may be the consequence of vasculitis (2, 3). Diagnostic and therapeutic procedures in cases with involved laryngotracheobronchial tree have to be executed with extreme caution since there is a high risk of complications and possibly fatal outcomes.

A significant percentage of RP patients have polyarthralgias/polyarthritis or oligoarthritis, with the wrist joints, metacarpophalangeal and proximal interphalangeal joints in the hands being most frequently involved, as well as the knees. Arthritis is frequently episodic, asymmetric, migratory, non-deforming, and mostly non-erosive, although associations with rheumatoid arthritis have been described as well (3).

Involvement of the eye is present in 20%–60% of patients, with different described manifestations in the form of proptosis, eyelid edema, episcleritis and scleritis, conjunctivitis, iridocyclitis, as well as possible retinopathy and optic neuritis. An early involvement of the eye has been considered as a marker of the serious, multisystem form of RP (3, 10, 12).

Dermatological manifestations have been described in 14%–37% of cases, most commonly in the form of changes resembling *erythema* nodosum or urticaria, in the form of purpura on the extremities, papules, *livedo reticularis*, superficial phlebitis or oral aphthous lesions (13). Changes affecting the skin are especially common in patients in whom RP is associated with myelodysplastic syndrome (10).

Other, rarer manifestations include cardiac, neurological and renal changes.

Cardiovascular (CV) manifestations of RP are present in 24%–52% of cases, representing the second most common cause of death in these patients. Valvular heart disease is the most common CV manifestation of RP, with the aortic valve being more frequently affected (10% of patients) than the mitral valve (2%–4%) (14). On the aortic valve, a dilation in the aortic root occurs, with aortic regurgitation, although the cases with aortic cusp rupture have been described, with a normal aortic root (3). The second most common cardiovascular manifestation is an acquired aneurysm of the thoracic aorta, developing in 5%–7% of patients with RP, with the aortic root and ascending thoracic portion being most frequently affected, while it rarely extends to involve major arterial blood vessels and abdominal aorta. The pathogenetic mechanism underlying the onset of aneurysm is slowly progressing aortitis with inflammation and gradual disruption of medial layers, carrying the risk of aortic rupture (10, 15). A systemic review of the literature, including the patients with polychondritis and involved aorta, including the thoracic and abdominal aorta, aortic valve and coronary arteries, has shown that aortic involvement (in the form of an aneurysm or ectasia) predominates, being present in 82% of patients, while aortic valve involvement has been reported in 36% (12). There have been descriptions of sporadic cases of atrioventricular block, including complete heart block, mitral regurgitation, acute pericarditis, myocarditis and silent myocardial infarction (3).

Vasculitis of any blood vessel is also possible, as well as RP associated with Takayasu's arteritis, *polyarteritis nodosa*, granulomatosis with polyangiitis and Churg–Strauss syndrome. The onset of arterial and venous thrombosis is thought to be the consequence of vasculitis or the presence of antiphospholipid antibodies.

In addition to CVS involvement, the kidney and central nervous system may be affected as well, although much less often. Kidney involvement can be the consequence of primary injury to the kidney, vasculitis or some other autoimmune disease. Renal failure has been reported in 10% of patients, and urine abnormalities in 26% of RP patients.

Vasculitis is the culprit when central and peripheral nervous system involvement is concerned, with the most common manifestations being headache, epileptic seizures, hemiplegia, aseptic meningitis, meningoencephalitis and cerebral aneurysm. Mononeuritis multiplex and cranial nerve paralysis may occur as well (3).

The prevalence of gastrointestinal involvement in RP patients is relatively low. However, in recent years there have been more and more cases of RP occurring in association with inflammatory bowel disease (IBD), including ulcerous colitis and Crohn's disease. In the literature, more than 1000 cases of RP have been described, out of which over 30 cases with accompanying IBD. The onset of arthralgias, eye involvement, aphthous lesions and *erythema nodosum* in both RP and IBD patients suggests a similar or identical autoimmune etiology of these diseases (16).

Diagnosis

RP is a rare disease which is difficult to recognize early in its course, especially when the typical involvement of the auricle and nose, or joint involvement is absent (3, 13, 17). The rate of misdiagnosis in RP reaches as high as 73%, and the time from the onset of first symptoms to diagnosis ranges from 2.9 to 5 years (18). It is necessary to emphasize the association of immune-mediated diseases, such as rheumatoid arthritis, spondyloarthritis, systemic lupus erythematosus, Sjogren's syndrome, vasculitis, antiphospholipid syndrome, inflammatory bowel disease, thyroiditis, Behcet's disease and others with RP in about 30% of cases (19). In addition to this overlapping with other diseases, the reasons for limited clinical investigations of RP are a very diverse clinical spectrum and low incidence of the disease (a couple of cases per one million people a year).

The diagnosis of relapsing polychondritis is based mostly on clinical disease parameters, while laboratory data play only a supportive role. There are no characteristic laboratory analyses for RP, although the inflammatory syndrome with elevated sedimentation and C-reactive protein (CRP) values is present (not persistently, though) in over 60% of patients (3, 20). Further, we may also encounter normocytic normochromic anemia, leukocytosis, thrombocytosis and polyclonal hypergammaglobulinemia. In some of the cases, antinuclear antibodies (ANA), antineutrophil cytoplasmic (ANCA) and antiphospholipid antibodies may be positive (3). Autoantibodies against collagen structures are not sensitive, nor specific enough, and thus have not entered clinical practice. Even the value of biopsy is rather limited, since positive findings have been reported in only two-thirds of the cases (19). Imaging methods are important in the assessment of the degree of systemic involvement and disease activity, especially computed tomography (CT), positron emission tomography—CT (PET-CT), and magnetic resonance imaging (MRI) (2).

In addition to establishing the diagnosis, it is necessary to assess disease activity and involvement and damage to the organs, and to establish or exclude the presence of other autoimmune diseases or a malignancy, since RP may appear as part of the paraneoplastic syndrome. The patient should be examined by an otorhinolaryngologist, pulmonologist, cardiologist (because of aortic and valvular involvement), hematologist (because of myelodysplastic syndrome). It is also necessary to check the renal function and perform an ANCA testing (19).

Three disease phenotypes with different clinical presentations have been recently described: hematological form in 10% of the cases; respiratory form in 25%; and mild disease form with a favorable prognosis in about 65% of the cases (19, 21).

The classification criteria for RP by Michet et al. require the presence of a proven inflammation in at least two of three auricular, nasal or laryngotracheal cartilages, or a proven inflammation in one cartilage, plus two of the other signs, including eye inflammation, vestibular dysfunction, seronegative arthritis or loss of hearing (4). The classification criteria should not be identified as diagnostic criteria—the diagnosis should be made based both on the classification criteria and the clinical experience of the practising physician.

Disease course and prognosis

RP is a chronic disease, commonly with a relapsing-remitting course. Poor prognostic factors include the onset of aortitis, vasculitis, eye involvement, and male gender is associated with a poor prognosis and higher prevalence of uveitis, loss of hearing, vestibular disorders, and a greater need for pulse doses of methylprednisolone and cyclophosphamide (19).

Although the survival of these patients has been significantly prolonged, the relapse rate is still very high, which is a substantial problem for both the patients and their doctors. In a study performed by Japanese authors, it has been shown that the risk factors for relapse are tracheal involvement, high pre-treatment values of CRP and initial monotherapy with prednisolone. The onset of relapse could possibly be prevented or delayed by the administration of combined therapy with prednisolone and immunosuppressants from the onset of the disease (22).

The principal causes of a lethal outcome are airway obstruction, CVS involvement and infections (6, 12, 17).

According to the information from 1986, the five-year survival of RP cases was 74%, and ten-year survival 55%, while according to the most recent information from 2016, these percentages were 95% and 91%, respectively. The improved survival percentages of RP patients are probably the consequence of earlier diagnosis, more effective and more aggressive treatments, and the availability of new immunosuppressive drugs, including the administration of biological agents. Renal disease significantly reduces ten-year survival rates to as low as 30% (6, 22, 23).

Therapy

Milder forms of RP should be treated with non-steroidal anti-inflammatory drugs and low doses of corticosteroids; the use of colchicine and dapsone is also possible. More severe disease forms should be treated with high doses of glucocorticoids and conventional immunosuppressants or biological agents (24). Conventional disease-modifying drugs (DMARDs) (methotrexate, azathioprine, cyclosporine, leflunomide, mycophenolate mofetil, cyclophosphamide) constitute the first line of treatment; in case of their failure or for more severe manifestations biological drugs may be used. The use of conventional DMARDs is also important because of the glucocorticoid-sparing effect (25).

Therapeutic approaches in RP are generally based on reports about individual cases and case series studies since as yet there have not been any randomized studies, as it is a very rare disease. There are no standardized guidelines for the treatment of RP, which means that the selection of drugs has to be empirical. In addition to the disease phenotype, the selection of drugs is also influenced by the presence of comorbid conditions, potential side effects and cost-effectiveness.

In a recent report by Petitdemange et al., an effectivity assessment has been done of conventional immunosuppressants and biological therapies used for RP based on the literature information. Anti-TNF drugs (infliximab and adalimumab, above all), tocilizumab and methotrexate have been shown to be the most effective DMARDs. A therapy of methotrexate

combined with some of these biological drugs is also recommended for the purpose of improving the effectiveness and in order to suppress the development of antibodies against the biological agent. The percentage of adequate responses was lower when anakinra and rituximab were used, while abatacept was used in a very small number of patients (24). So far, there has been very little data about the use of JAK inhibitors. When biological agents are used, there is an associated risk of adverse effects, especially infections. Despite an aggressive treatment approach and use of biological drugs, a French study has demonstrated that disease remission, i.e. complete response in the first 6 months of treatment, is achieved in only 19% of patients (26). A recent study has shown that most RP patients demonstrate persistent disease activity despite the treatment (27).

In life-threatening situations encountered in RP patients, the use of cyclophosphamide is indicated, since this agent can produce a rapid therapeutic response (24).

A treatment of eye involvement with developed necrotizing scleritis is rather hazardous, since it may lead to eye perforation. It is therefore necessary that the patient be examined by an ophthalmologist, receiving if required pulse doses of methylprednisolone and cyclophosphamide or biological agents, while a topical treatment can suffice only in mild cases of episcleritis (19).

In 25% of cases with airway involvement, a laryngotracheal stricture will develop, and therefore signs of tracheobronchomalacia should be sought for early during the disease course. Lung fibroscopy should be strictly avoided in RP patients because of the risk of tracheal perforation.

Corticosteroids and immunosuppressants are not effective in the treatment of more advanced forms of aortic and valvular involvement—they should be treated surgically (10).

Conclusion

RP is a rare systemic disease with the incidence of several cases per one million people a year and insufficiently clarified etiopathogenesis, affecting the elastic, hyaline and fibrous cartilages and proteoglycan-abundant tissues, such as the eye, blood vessels, heart and inner ear. It is characterized by a diverse clinical picture with accompanying constitutional symptoms, and its diagnosis is usually significantly delayed. In 30% of cases, it is associated with other autoimmune and malignant diseases. Involvement of the laryngotracheal tree, cardiovascular manifestations and secondary infections are the most common causes of lethal outcomes. Despite an aggressive treatment approach, use of corticosteroids and conventional and biological DMARDs, the disease may demonstrate a persistent activity and produce complications. The treatment is nowadays empirical, and for better control of the disease in the future, randomized controlled studies on a larger number of patients are required.

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RELAPSNI POLIHONDRITIS: OD ETIOPATOGENEZE DO TERAPIJE

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Relapsni polihondritis (RP) jeste retka autoimuna sistemska bolest, nedovoljno poznate etiopatogeneze, uglavnom relapsno-remitentnog toka, a zahvata elastičnu, hijalinu i fibroznu hrskavicu i tkiva bogata proteoglikanima. Može dovesti do anatomskog i funkcionalnog oštećenja, a uprkos lečenju, i do fatalnog ishoda. Najčešće se manifestuje u vidu aurikularnog i nazalnog hondritisa i poliartritisa. Zahvatanje laringotraheobronhijalnog stabla, kao i srčanih zalistaka i aorte, uz pojavu sekundarne infekcije – pre svega donjih delova respiratornog trakta – najčešći su uzroci letalnog ishoda. U mogući klinički spektar RP-a spadaju: zahvatanje oka episkleritisom, skleritisom i dr., unutrašnjeg uha vestibularnim poremećajima i pojava senzoneuronalnih simptoma,kao i zahvatanje centralnog i perifernog nervnog sistema. Uglavnom se značajno kasni sa postavljanjem dijagnoze, za koju je najbitnija klinička prezentacija, dok su laboratorijski nalazi od suportivnog značaja; *imaging* metode (CT, PET-CT, MR) važne su pak za procenu aktivnosti bolesti. Blaže oblike RP-a treba lečiti primenom nesteroidnih antiinflamatornih lekova i malim dozama kortikosteroida, dok se teži oblici leče primenom većih i, ukoliko je to potrebno, pulsnih doza kortikosteroida, kao i konvencionalnim i biološkim lekovima za modifikaciju bolesti. Uznapredovali oblici bolesti aorte i srčanih zalistaka zahtevaju hirurško lečenje.

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