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Relapsing polychondritis: A 2016 update on clinical features, diagnostic tools, treatment and biological drug use

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A B S T R A C T

Relapsing polychondritis (RP) is a very rare autoimmune disease characterised by a relapsing inflammation of the cartilaginous tissues (joints, ears, nose, intervertebral discs, larynx, trachea and cartilaginous bronchi), which may progress to long-lasting atrophy and/or deformity of the cartilages. Non-cartilaginous tissues may also be affected, such as the eyes, heart, aorta, inner ear and skin. RP has a long and unpredictable course. Because no randomised therapeutic trials are available, the treatment of RP remains mainly empirical. Minor forms of the disease can be treated with non-steroidal anti-inflammatory drugs, whereas more severe forms are treated with systemic corticosteroids. Life-threatening diseases and corticosteroid-dependent or resistant diseases are an

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indication for immunosuppressant therapy such as methotrexate, azathioprine, mycophenolate mofetil and cyclophosphamide. Biologics could be given as second-line treatment in patients with an active disease despite the use of steroids and immunosuppressive drugs. Although the biologics represent new potential treatment for RP, very scarce information is available to draw any firm conclusion on their use in RP.

Introduction

Relapsing polychondritis (RP) is a rare autoimmune disease mostly, but not exclusively, affecting the hyaline, elastic and fibrous cartilaginous tissues [1–5].

Pathogenesis

The pathophysiology of RP remains largely unknown. Several features, however, suggest that RP is an autoimmune disorder. The inflammatory infiltrate in the affected tissue is polymorph and consists of lymphocytes (mainly CD4+ T cells), macrophages, neutrophils and plasma cells. Infiltration of tissues by different cellular and molecular inflammatory mediators leads to the release of degradative enzymes such as matrix metalloproteinase and reactive oxygen metabolites by inflammatory cells and chondrocytes, and ultimately to the destruction of cartilage and other proteoglycan-rich tissues [6].

The main hypothesis of the pathophysiology of RP is an autoimmune reaction initially directed against the cartilage, further spreading to non-cartilaginous tissues [6]. The initiating mechanism could be damage to the cartilage, exposing immunogenic epitopes of the chondrocytes or extracellular cartilage matrix [6]. Development of RP following piercing of the cartilage portion of the pinna of the ear [7] and ingestion of glucosamine chondroitin supplement [8] supported this hypothesis. The initial auto-antigens seem indeed to be components of the cartilage. For example, injection of type-II collagen into rats can induce auricular chondritis [9,10]; immunisation of mice with certain HLA-DQ molecules along with type-II collagen can also cause auricular chondritis and polyarthritis [11,12]; and injection of matrilin-1, a specific tracheal cartilage protein, into rats reproduces the respiratory lesions of RP [13]. As in some other autoimmune disorders, susceptibility to RP has been reported to be significantly associated with the presence of HLA-DR4 [14,15]. The extent of organ involvement in RP appears to be negatively associated with HLA-DR6 [15].

Autoantibodies against cartilage, collagen (mostly type II, including other types – IX, X, and XI), matrilin-1 and cartilage oligomeric matrix proteins (COMPs) have been found in patients with RP [6,16–18]. The diagnostic value of these autoantibodies is extremely poor as they are found in a limited number of patients and they are not specific to RP. For example, serum type-II collagen antibodies, which are found in approximately 30% of patients with RP, can also be detected in rheumatoid arthritis [16,19]. Autoreactive T lymphocytes specific to collagen have also been found in RP [20]. T lymphocytes in RP have a Th1 profile, i.e. the majority of them produce interferon-gamma [21].

The levels of serum monocyte chemoattractant protein 1 (MCP-1), macrophage inflammatory protein 1-beta (MIP-1beta) and interleukin-8 (IL-8) are increased during flares of the disease, highlighting the role of monocytes and macrophages, and their recruitment into injured tissues [22].

Epidemiology

The rarity of RP makes epidemiological data very scarce. Its incidence is poorly documented and probably underestimated. An estimated incidence of 3.5 cases per million people has been reported in a study in Rochester (Minnesota, USA) [2]. A prevalence study by the Department of Defense beneficiary population leads to an evaluation of 4.5 cases per million [23]. In a recent UK study, the prevalence of RP was 9.0 (95% confidence interval (CI) 7.6–10.5) per million and its incidence was 0.71 (95% CI 0.55–0.91) per million per year [24].