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Review

Pathogenesis of relapsing polychondritis: A 2013 update

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ABSTRACT

Relapsing polychondritis (RP) is a systemic inflammatory disease primarily affecting not only the cartilaginous structures of the ears, nose and tracheobronchial tree but also the joints, the inner ear, the eyes, and the cardiovascular system. RP is an immune-mediated disease during which target antigens are still unknown, but data from human studies and murine models strongly support a role of both Collagen Type II (CII) and matrilin-1 as potential candidates. RP is likely a Th1-mediated disease as serum levels of interferon (IFN)-γ, interleukin [IL]-12, and IL-2 parallel changes in disease activity, while the levels of Th2 cytokines do not. Serum levels of sTREM-1, interferon-γ, CCL4, vascular endothelial growth factor, and matrix metalloproteinases-3 are significantly higher in RP patients than in healthy donors, with sTREM-1 correlating with disease activity. Patients with active RP also have significantly higher levels of MCP-1, MIP-1β, MIF, and IL-8 than controls. These pro-inflammatory chemokines are involved in the modulation and recruitment of monocytes and neutrophils. Altogether, these data suggest that a complex cytokine network orchestrates the recruitment of infiltrating cells in RP lesions. Cytokine modulation using TNFα blockers, rituximab, anakinra, tocilizumab, and abatacept has recently been shown effective in some RP cases but further data are needed. Better understanding of the repertoire of infiltrating cells may provide interesting clues to further define the putative RP auto-antigens. Study of circulating mononuclear cells during RP flares may also provide crucial information about the ongoing cellular trafficking and recruitment processes involved in this rare disease.

Contents

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1. Introduction

Relapsing polychondritis (RP) is a systemic inflammatory disease primarily affecting not only the cartilaginous structures of the ears, nose and tracheobronchial tree but also the joints, the inner ear, the eyes, and the cardiovascular system [1]. The first case of relapsing polychondritis was described in 1923 by Jaksch-Wartenhorst [2], but little attention was given to the entity until the 60s, when Pearson et al. introduced the name "relapsing polychondritis" [3]. Currently, diagnosis of RP relies mostly on the criteria established by Michet et al. [4] which require the presence of a proven inflammation in at least 2 of 3 of the auricular, nasal, or laryngotracheal cartilages, or the proven inflammation in one of these cartilages plus 2 other signs, including ocular inflammation, vestibular dysfunction, seronegative inflammatory arthritis, or hearing loss (Table 1). RP is a flaring-remitting disease, and a collaborative international score for assessing disease activity in RP has been recently developed [5]. The exact cause of RP is still unknown but the disease is mostly seen as an immune-mediated disease, as there is a well-documented overlap of RP with other rheumatic and autoimmune diseases [4,6,7]. RP is strongly associated with the HLA allele DR4, and various immune responses directed against cartilage components have been demonstrated in RP patients. In this article we review the most updated data regarding the etiology and pathogenesis of RP, including the role of the genetic susceptibility to the disease and the data obtained in animal models.

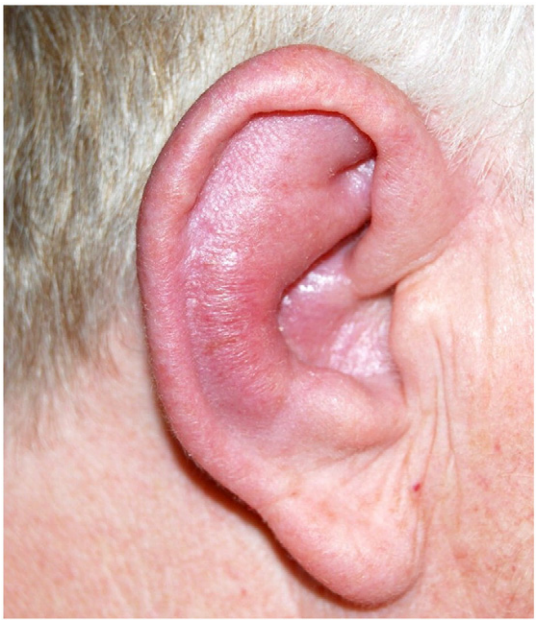

Fig. 1. Auricular chondritis. Typical swelling, erythema, and tenderness of the cartilaginous part of the ear, sparing the lobule which lacks cartilage.

2. Pathology of RP

Auricular chondritis is one of the hallmarks of RP, as it is seen in 90–95% of patients [4,6]. Physical examination typically reveals swelling, erythema, and tenderness of the cartilaginous part of the ear, sparing the lobule which lacks cartilage (Fig. 1). Because of the rarity of the disease, only limited microscopic data are available in the literature [8]. Early RP lesions seem to be characterized by a pleomorphic infiltrate with various proportions of lymphocytes, macrophages, neutrophils, and plasma cells in the perichondrium, while the cartilage is mostly normal at this initial stage [9]. Infiltrating T lymphocytes are mainly CD4+ T cells [10,11]. The antigen-presenting cells found in the inflamed perichondrium are activated, as attested by the expression of the HLA-DR marker [11]. Direct immunofluorescence examination show inconstant deposits of immunoglobulins (Ig) and C3 at the junction between the perichondrium and the cartilage [12]. As the disease progresses, the cartilage is invaded by inflammatory cells. At that stage, proteolytic enzymes such as Matrix metalloproteinase (MMP)-3 and cathepsins K and L are highly expressed [10] and the chondrocytes are surrounded by lysosomes [13]. MMP-8, MMP-9, and elastase are detected only in the perichondral granulation, whereas MMP-3 and cathepsins K and L are detected in both chondrocytes and granulations [14]. Consistent with these data, whole-blood gene expression analysis reveals a strong expression of the MMP-9 gene [15]. The cartilage is being progressively destroyed and loses its basophilia as the glycosaminoglycans are degraded [16–18]. The elastic and collagen fibers are disorganized and fragmented [19,20]. The chondrocytes eventually appear pycnotic and undergo apoptosis [10,14]. Immunofluorescence show Ig and C3 deposits in the matrix. Eventually, the cartilage matrix is severely destroyed and replaced by a fibrous connective tissue. Gelatinous cysts and regions of calcification may be observed. Macroscopically, the shape of the cartilage may be severely impaired [19] with the development of cauliflower ears (Fig. 2), saddle nose deformity or even fatal airway collapse [21].

Table 1
Michet criteria for relapsing polychondritis [4].

Proven inflammation in 2 of 3 of the auricular, nasal, or laryngotracheal cartilages.
Or,
Proven inflammation in 1 of 3 of the auricular, nasal, or laryngotracheal cartilages plus 2 other signs including ocular inflammation, vestibular dysfunction, seronegative inflammatory arthritis, and hearing loss.

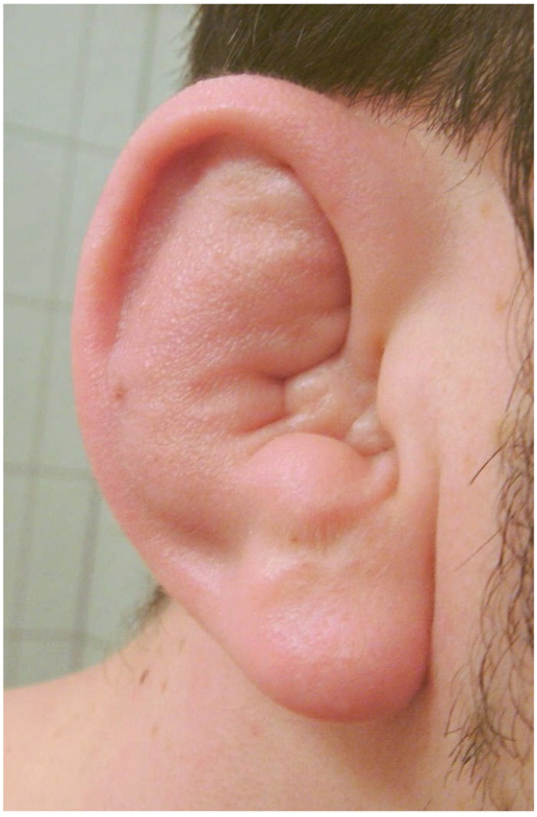

Fig. 2. Cauliflower ear. Severe ear impairment with thickened skin and fixed deformities.