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Review

Relapsing polychondritis: A clinical update

Lucia Longo [a], Antonio Greco [b], Andrea Rea [a], Vincenza Rita Lo Vasco [c], Armando De Virgilio [b,*], Marco De Vincentiis [b]

[a] Department Organs of Sense, Phoniatrics Section, 'Sapienza' University of Rome, Viale del Policlinico 155, 00100 Roma, Italy
[b] Department Organs of Sense, ENT Section, 'Sapienza' University of Rome, Viale del Policlinico 155, 00100 Roma, Italy
[c] Department Organs of Sense, 'Sapienza' University of Rome, Viale del Policlinico 155, 00100 Roma, Italy

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ABSTRACT

Relapsing polychondritis (RP) is a rare connective tissue disease in which recurrent bouts of inflammation, involve the cartilage of the ears, nose, larynx, tracheobronchial tree and cardiovascular system. RP is generally observed in the fourth and fifth decades of life and occurs with equal frequency in both sexes. The cause of RP is still unknown. It is considered an immune-mediated disease, as there is an overlap between well documented RP with other rheumatic and autoimmune diseases. There is a significant association of RP with the antigen HLA-DR4. RP includes loss of basophilic staining of cartilage matrix perichondral accompanied by inflammation of the cartilage. Cells are present perivascular mononuclear and polymorphonuclear cells infiltrated. The chondrocytes become vacuolated and necrotic and are replaced by fibrous tissue.

Common symptoms are often absent in the early stages of the disease in almost half the cases, resulting in delay in diagnosis. The development of chondrite allows the diagnosis of RP in patients initially evaluated for joint abnormalities, ocular, cutaneous, or audio-vestibular.

Diagnostic criteria for RP are based on characteristic clinical manifestations. According to Damiani and Levine, the diagnosis can be considered final when one or more of the clinical features are present in conjunction with biopsy confirmation. The course of symptoms for patients with relapsing polychondritis is often unpredictable.

Patients with mild signs of acute inflammation are usually treated with non-steroidal anti-inflammatory drugs and small doses of prednisone. Patients with severe manifestations, such as airway compromise may require high doses of prednisone or even intravenous pulse methyl-prednisone.

Contents

1. Introduction

The first case of relapsing polychondritis (RP) was described in 1923 by Jaksch-Wartenhorst [1]. The term "relapsing polychondritis" was

* Corresponding author. Tel: +39 380 3408909; fax: +39 06 49976803.
E-mail address: armando.devirgilio@gmail.com (A. De Virgilio).

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first used by Pearson et al. in 1960 [2]. RP is a rare connective tissue disease in which recurrent bouts of inflammation, involve the cartilage of the ears, nose, larynx, tracheobronchial tree and cardiovascular system. RP was considered as a degenerative disease. Recurrent bouts of inflammation lead to the permanent destruction of these structures. Cardiovascular and respiratory complications of RP are associated with high morbidity and mortality. RP is a systemic disease, as shown by the frequent presence of arthritis, ocular inflammation, audiovestibular involvement, skin lesions, heart valve incompetence, and vasculitis. Thus, patients with

RP present with a wide spectrum of clinical symptoms and signs that often raise major diagnostic dilemmas.

Patients usually consult primary care physicians, otolaryngologists, rheumatologists and ophthalmologists. On average, it takes 3 years between occurrence of the first symptom until RP is diagnosed.

2. Epidemiology

RP is generally observed in the fourth and fifth decades of life and appears to occur with equal frequency in both sexes [3–6]. RP predominantly affects middle-aged adults, with a slight female preponderance [7–11]. No apparent differences between the ethnic groups [9,10] were reported, and there were some cases of RP in the very young and elderly [11,12].This disorder is estimated to occur with an incidence of 3.5 per million/year [13,14].

3. Etiopathogenesis

To date, the etiology of RP is still unknown, but the pathogenesis should involve an autoimmune reaction to type II collagen, present in the cartilage and in the sclera. In fact, anti-cartilage antibodies are detected in at least 33% of RP patients, and their titers appear to correlate with disease severity. [15,16] It is considered an immune-mediated disease, as there is an overlap between well documented RP and other rheumatic and autoimmune diseases [3–5,7–10,17–19]. Although a large number of cases have been reported recently, and the knowledge of the clinical features, pathogenesis, and management of the RP has increased considerably, the literature data available are very limited [5,20].

The histological features of RP include loss of basophilic staining of cartilage matrix perichondral accompanied by inflammation of the cartilage. Cells are present perivascular mononuclear and polymorphonuclear cells infiltrated. The chondrocytes become vacuolated and necrotic and are replaced by fibrous tissues (Fig. 1) [18,21].

In humans, the destruction of cartilage is derived from the release of degradative enzymes, including matrix metalloproteinases and reactive oxygen metabolites by inflammatory cells, chondrocytes and other cell components. The release of these enzymes is probably secondary to immune activation mediated by chondrocytes, by cytokines and other inflammatory cells including interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-a) [22].

However, autoimmunity is involved in several ways:

1) The inflammatory infiltrate tissue is composed of macrophages, CD4 + cells and B. In addition, deposition of immunoglobulins and complement components is evident in tissue lesions of patients with RP [23].
2) Antibodies directed against the type II collagen, as well as collagen type IX and XI are found in the serum of patients with RP [24]. T cell clones isolated from a patient with RP were found to be specific for the type II collagen peptide [21,25].
3) Immunization of rodents with collagen II and the immunization of rats with cartilage matrix protein (matrillin-1) result in the development of ear chondrite and tracheal cartilage inflammation, respectively [26–28].
4) Autoimmunity has been reported in association with autoimmune diseases and HLA class II (DR4).
5) The tissue specificity of RP suggests that antigens derived from cartilage play an important role in guiding and spreading the disease [23].

In a genetically predisposed individual, an unknown factor x can cause an immune response to tissue rich in collagen type II and matrillin-1 [26–28]. This is responsible for the inflammation of the cartilage, resulting in the production of cytokines and autoantibodies and the perpetration of an immune response. This process can damage the chondrocytes, release proteolytic enzymes, and lead to the destruction of cartilage and the expression of the disease.

A significant association of RP with the antigen HLA-DR4 was recently discovered. There was no predominance of one of the DRB1 * 04 alleles subtype of these patients [29]. In addition, no association was found in HLA-DR1. This contrasts with RA, which has established a clear association with DRB1 * 0401 and DRB1 * 0404 [29].

4. Symptoms and signs

Clinical manifestations of RP are highly variable. Common symptoms are often absent in the early stages of the disease in almost half the cases, resulting in delay in diagnosis. The development of chondrite allows the diagnosis of RP in patients initially evaluated for joint abnormalities, ocular, cutaneous, or audiovestibular. In patients with chondrite, the fin is the most common site of involvement. Unexplained prolonged fever may be the presenting symptom of RP.

Auricular chondrite is specific to RP. It is present in 20% of patients at the onset of the disease and in 90% [22] during the course of the disease. One or both ears can be affected. The entire hall is swollen, red, or less often purplish, hot, and painful even at the slightest contact. The ear lobe, which does not contain the cartilage, is spared (Fig. 2) [7,30]. These events last a few days or, more rarely, a couple of weeks and

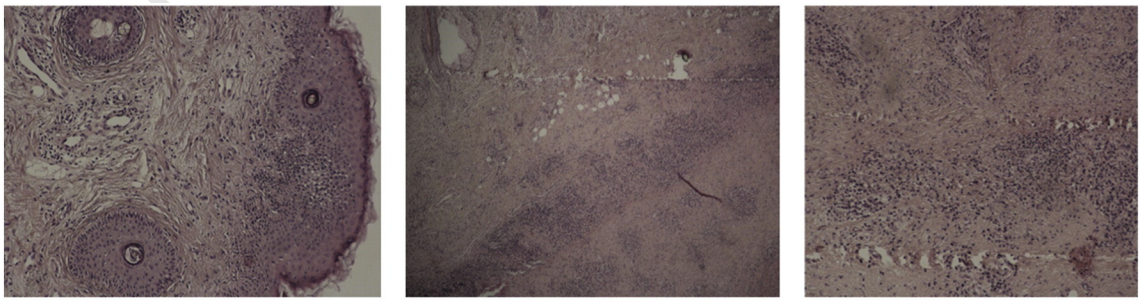

Fig. 1. (a) The dermis contains a mild focal lymphohistiocytic infiltrate. H&E, ×100. (b) Degenerative and inflammatory changes affecting the marginal chondrocytes with loss of basophilia and poor alcian blue staining of the cartilaginous tissue. H&E, ×40. (c) The inflammatory cells infiltrate, and lymphocytes, plasma cells, and histiocytes, infiltrate the degenerative cartilage. H&E, ×100. From: Sosada B, Loza K, Bialo-Wojcicka E. Relapsing polychondritis. Case Rep Dermatol Med 2014;2014:791951.