Journal of Autoimmunity 48-49 (2014) 53–59

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Diagnosis and classification of relapsing polychondritis

Luca Cantarini [a,*,1], Antonio Vitale [a,1], Maria Giuseppina Brizi [a], Francesco Caso [a,b], Bruno Frediani [a], Leonardo Punzi [b], Mauro Galeazzi [a], Donato Rigante [c]

[a] Interdepartmental Research Center of Systemic Autoimmune and Autoinflammatory Diseases, Rheumatology Unit, Policlinico Le Scotte, University of Siena, Siena, Italy
[b] Rheumatology Unit, Department of Clinical and Experimental Medicine, University of Padova, Padova, Italy
[c] Institute of Pediatrics, Università Cattolica Sacro Cuore, Rome, Italy

ARTICLE INFO

Article history:
Received 7 October 2013
Accepted 13 November 2013

Keywords:
Relapsing polychondritis
Cartilage disorder
Type II collagen

ABSTRACT

Relapsing polychondritis is a rare and potentially fatal autoimmune disease of unknown etiology, characterized by inflammation and destruction of different cartilaginous structures, including the ear, nose, larynx, trachea, bronchi, peripheral joints, eye, heart and skin, with high risk of misdiagnosis. The spectrum of clinical presentations is protean and may vary from intermittent episodes of painful and disfiguring auricular and nasal chondritis or polyarthritis to severe progressive multi-organ damage. A laryngotracheobronchial involvement appears in nearly half of patients and is complicated by local obstructions, which may be life-threatening. A highly medical specialized approach is required for diagnosis of relapsing polychondritis. This review comprehensively examines the literature related to the clinical sceneries of the disease and focuses on both diagnostic tools used in clinical studies and recent findings related to its etiopathogenesis.

Relapsing polychondritis (RP) is an uncommon autoimmune disorder characterized by widespread, destructive, inflammatory lesions of cartilaginous and different connective tissue structures: its clinical manifestations include recurrent chondritis of ears, nose, larynx and tracheobronchial tree, which might lead to floppy ears, saddle nose, and laryngotracheal stenosis in advanced cases. However, all types of cartilage may be involved, such as the hyaline cartilage of peripheral joints and the fibrocartilage of extra-articular sites, as well as proteoglycan-rich tissues including the media of the arteries, the conjunctiva and sclera of the eye [1].

1. History and epidemiology

RP was firstly described by Jaksch-Wartenhorst in 1923 with the name "polychondropathia" [2]; in 1960 Pearson et al. suggested the name "*relapsing polychondritis*" to highlight its episodic and recurrent nature [3]. In 1976 McAdam et al. proposed the first diagnostic criteria for RP [4], later expanded by Michet et al. [5]. This disorder is estimated to occur with an incidence of 3.5 per million/year [6,7], and affects all ethnic groups, though a predominance in the Caucasian population has been noted [1]. The peak age at disease onset is the fifth decade of life [1,4,5], but RP may appear during childhood and as late as the eighth decade [8–11]. As regards sex distribution, the male-to-female ratio has been estimated to be between 1:2.5 and 1:3 [1,11], while other studies reported no differences among genders [4,5]. The association with other autoimmune disorders, myelodysplasia and/or systemic inflammatory conditions is found in 25–30% of adult patients with RP [8,12].

2. Etiology and pathogenesis

RP does not appear as a familiar disease, although an association with HLA-DR4 has been described, and the extent of organ involvement has been found negatively associated with HLA-DR6 [12]. Other examinations evaluating HLA class II allelic distributions showed some significantly increased allele frequencies in RP patients, suggesting that immunological mechanisms might play a relevant role in the disease pathogenesis [13].

Firstly, the main pathogenetic hypothesis was that clinical manifestations were secondary to a vasculitis. However, it was unclear whether vascular inflammation was an associated sign or the cause of RP itself [4]. To date, the etiology of RP is not clearly defined, but the pathogenesis should involve an autoimmune

* Corresponding author. Rheumatology Unit, Policlinico Le Scotte, University of Siena, Viale Bracci 1, 53100 Siena, Italy. Tel.: +39 (0) 577 586776; fax: +39 (0) 577 40450.
E-mail address: cantariniluca@hotmail.com (L. Cantarini).
[1] These authors contributed equally to this manuscript.

0896-8411/$ – see front matter © 2014 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jaut.2014.01.026

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 [14,15]. In addition, auricular chondritis similar to that observed in human RP can be induced in mice and rats by immunization with native type II collagen [16,17]. Since titers against the native type II collagen were substantially higher than titers against constituent alpha-1 (II) chains, Foidart et al. argued that the formation of antibodies to type II collagen might represent a primary event in the pathogenesis of RP and not a consequence of cartilage destruction [15]. Moreover, circulating antibodies against corneal epithelium were also determined, providing further evidence for an autoimmune origin of the disease [18]. Later, Alsalameh et al. found parallel humoral and cellular immune reactivities against collagens type IX and XI, in combination with collagen type II, believing that these observations were epiphenomena resulting from a specific cartilage damage [19].

Alternatively, an autoimmune response in RP patients can be driven also by antibody production and T cell response against matrilin-1, a cartilage matrix protein prominent in tracheal, auricular, and nasal cartilages [20,21].

Anyway, the autoimmune pathogenesis is hypothetically induced by different noxae (such as trauma, toxins or infectious agents), which lead to the exposure of connective tissue or cell membrane self-epitopes in genetically susceptible individuals [22]. The subsequent inflammatory response would perpetuate enzymatic and oxygen metabolite-mediated connective tissue degradation [23]. Cytokines released during this inflammatory process can both amplify the pathologic process, and induce constitutional symptoms. In particular, tumor necrosis factor-α can induce synthesis and release of matrix-degrading proteinases from chondrocytes [15].

3. Clinical manifestations

In over 80% of patients RP is disclosed by auricular chondritis and polyarthritis, though every organ can be involved. Constitutional symptoms including fever, weight loss, night sweats, fatigue and lymphoadenomegaly have been largely documented [1,12].

Auricular chondritis might occur as an isolated clinical sign, characterized by inflammation of the cartilaginous portion of the pinna, with pain, redness, swelling or tenderness, leading to a nodular or verrucous appearance and becoming soft and flabby after repeated attacks, or sometimes after a single prolonged episode. The disease typically spares the auricular lobe, which has no cartilage. The inflammation of the external auditory meatus and Eustachian tube can lead to otitis media and result in conductive hearing loss. However, also vestibular symptoms or sensorineural involvement are possible as a result of inflammation of the vestibular structures or vasculitis in the vestibular or cochlear branch of the internal auditory artery [1,4,24].

Nasal pain, hoarseness, throat pain, and difficult talking are also common presenting symptoms of RP [25]. According to Isaak et al., nasal cartilage involvement is present at the time of diagnosis in 24% of patients, subsequently developing in 54% of cases [26]. The inflammatory process is painful and sometimes followed by mild epistaxis or serosanguinous exudation: it can destroy the nasal cartilage, leading to flattening of the nasal bridge or the tip, and resulting in a saddle nose deformity or a flat nasal tip in late-phases. Saddle nose seems to be more common in patients who are less than 50 years and in females [1,5,26].

A laryngotracheobronchial disease appears in nearly half of RP patients, being complicated by laryngeal, tracheal, and/or bronchial obstructions, which may be severe and life-threatening also in the earliest phases [4,27]. Other common symptoms include pain and tenderness over the thyroid cartilage and trachea, hoarseness, nonproductive cough, dyspnea, stridor, and wheezing [1,28]. Strictures in the airways from chronic inflammation, fixed or dynamic, might also generate subglottic inflammation, tracheal collapse, and secondary pulmonary infections [1,5,26]. Airway complications truly represent the main cause of death among RP patients [5]. Pulmonary infiltrates, probably related to an underling vasculitis, may accompany RP [26].

Polyarthralgia and/or polyarthritis or oligoarthritis mainly affecting the metacarpophalangeal/proximal interphalangeal joints, knees and wrists, may be the presenting symptoms in 33% of patients with RP [29]. Arthritis is often episodic, asymmetric, migratory, non-deforming: all synovial joints may be virtually involved [30]. Arthritides may appear in 50–85% of patients with RP [1] and are generally non-erosive in nature. However, Isaak et al. found that approximately 30% of patients with RP develop an erosive arthropathy associated with rheumatoid arthritis [26].

Ocular manifestations occur in approximately 60% of patients with RP [12,26,31,32]. Major ocular complications include proptosis, lid edema, episcleritis/scleritis, conjunctivitis, corneal infiltrates/thinning, iridocyclitis, retinopathy, and optic neuritis [4,33–37]. Vasculitis involving the extraocular muscles has been also reported [38]. The eyes are sometimes the initial site of involvement and, since most patients with ocular inflammation tend to develop multiple systemic manifestations, it may be regarded as a marker of severity [39]. Interestingly, Lichauco et al. described a patient who presented with exophthalmos and later revealed an orbital mucosa-associated lymphoid tissue (MALT)-type B cell lymphoma. The authors hypothesized that the lymphoma resulted from a malignant transformation of the RP-induced inflammatory pseudotumor, and emphasized that neoplastic diseases should be considered in the differential diagnosis of RP patients presenting with proptosis [40].

Dermatologic manifestations have been described in 35–50% of RP cases, and cutaneous abnormalities can even be the first feature in 12% of patients [41]. Nodules on the limbs and purpura are the most common signs of skin involvement. There have been reports of urticarial-like lesions in RP, typically associated with vasculitis, erythema multiforme, erythema annulare centrifugum [42], erythema elevatum diutinum [43], skin panniculitis [41], actinic granulomas [44], and Sweet's syndrome [45].

Other less frequent manifestations include cardiac, neurologic and renal diseases.

Cardiovascular manifestations of RP are present in 24–52% of patients [46] and represent the second most common cause of death in these patients [1,5]. Cardiac involvement is more prominent in males and requires a more invasive approach [47,48]. The most common manifestation of cardiovascular involvement is valvular heart disease, which can also occur despite apparent RP remission [49]. The aortic valve is affected more frequently than the mitral valve, resulting in aortic root dilation and aortic regurgitation [4,5,50,51]. However, cusp rupture with normal aortic root has also been reported [52]. Aortic aneurysms occur frequently in RP, may be multiple and involve all parts of the aorta, even resulting in fatal rupture in asymptomatic patients [53]. Furthermore, several cases of atrioventricular block, comprising complete heart block, mitral regurgitation, obstructive lesions, acute pericarditis, myocarditis, and silent myocardial infarction have been reported [5,26,50,54,55]. In addition, vasculitis of any vessels may be seen in RP patients and may be local or systemic, painless or fulminant. The association between RP and Takayasu's arteritis [56], polyarteritis nodosa [57,58], granulomatosis with polyangiitis [57] and Chürg-Strauss syndrome [59,60] have been described as well. The arterial and venous thrombosis reported in RP may be due either to vasculitis or to the presence of anti-phospholipid antibodies [61].