Relapsing polychondritis

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Creation Date: November 2001
Update: October 2004

Scientific Editor: Professor Haralampos M. Moutsopoulos

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Abstract
Relapsing polychondritis (RP) is a multisystem inflammatory disease of unknown etiology affecting the cartilage. It is characterized by recurrent episodes of inflammation affecting the cartilaginous structures, resulting in tissue damage and tissue destruction. All types of cartilage may be involved. Chondritis of auricular, nasal, tracheal cartilage predominates in this disease, suggesting response to tissue-specific antigens such as collagen II and cartilage matrix protein (matrillin-1). The patients present with a wide spectrum of clinical symptoms and signs that often raise major diagnostic dilemmas. In about one third of patients, RP is associated with vasculitis and autoimmune rheumatic diseases. The most commonly reported types of vasculitis range from isolated cutaneous leucocytoclastic vasculitis to systemic polyangiitis. Vessels of all sizes may be affected and large-vessel vasculitis is a well-recognized and potentially fatal complication. The second most commonly associated disorder is autoimmune rheumatic diseases mainly rheumatoid arthritis and systemic lupus erythematosus . Other disorders associated with RP are hematological malignant diseases, gastrointestinal disorders, endocrine diseases and others. Relapsing polychondritis is generally a progressive disease. The majority of the patients experience intermittent or fluctuant inflammatory manifestations. In Rochester (Minnesota), the estimated annual incidence rate was 3.5/million. The peak age for disease onset is the fifth decade, although cases have been reported at both extremes of life. The treatment of choice is prednisone; however, immunosuppressive drugs seem to have an additional value. Methotrexate was found to be an efficacious and well-tolerated steroid sparing drug.

Keywords
Relapsing polychondritis; cartilage; chondritis; auricular; nasal; laryngotracheal; collagen type II; matrillin-1; vasculitis; autoimmune diseases; malignant disorders.

Disease name and synonyms
Relapsing polychondritis;
auricular chondritis;
nasal chondritis;
polychondropathia.

Diagnostic criteria / Definition

Relapsing polychondritis (RP) was first described in 1923 by Jaksch-Wartenhorst under the term of "polychondropathia" and was considered as a degenerative disease (1). It is an uncommon multisystemic disorder of unknown etiology affecting young adults. It is characterized by recurrent episodes of inflammation affecting the cartilaginous structures, resulting in tissue damage and tissue destruction. All types of cartilage may be involved such as: the elastic cartilage of the ears and nose, the hyaline cartilage of peripheral joints, the fibrocartilage of the axial skeleton and the cartilage of the tracheobronchial tree. RP can also affect other proteoglycan-rich structures like the eye, heart, blood vessels and inner ear. Thus, patients with RP present with a wide spectrum of clinical symptoms and signs that often raise major diagnostic dilemmas (2-5).

In the majority of patients, RP has a fluctuating but progressive course in which recurrent bouts of inflammation lead to the permanent destruction of the involved structures. 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. This gap reflects the diagnostic ambiguities that may encountered. Thus, proposed diagnostic criteria for RP are based on characteristic clinical manifestations.

Empirical diagnostic criteria have been established by McAdam *et al.* (6), Michet *et al.* (7) and Damiani *et al.* (8). The diagnostic criteria proposed by McAdam require three or more clinical features, even without biopsy confirmation (Table 1). Damiani and Levine have suggested that diagnosis can be considered as definitive when one or more of the clinical features are present in conjunction with biopsy confirmation.

Table 1. Diagnostic criteria for relapsing polychondritis (6)

Recurrent chondritis of both auricles
Non erosive inflammatory polyarthritis
Chondritis of nose cartilage
Inflammation of ocular structures
keratitis, scleritis, episcleritis, uveitis
Chondritis of the respiratory tract
laryngeal and/or tracheal cartilages
Cochlear and/or vestibular damage causing sensor neural hearing loss, tinnitus and/or vertigo

Differential diagnosis

Although the clinical features of this disease are characteristic, diagnosis may be difficult in some cases. Thus, acute streptococcal infection, fungal infection, Hansen disease, and syphilis may all lead to perichondritis that can be easily misdiagnosed as RP. Auricular involvement must also be differentiated from traumatic and chemical conditions, such as frostbite and insect bite. Prolonged endotracheal intubation may cause tracheal injury similar to that of RP (5-8). Nasal damage may occur in many other conditions such as local infections from fungi, tuberculosis, syphilis, leprosy, Wegener's granulomatosis and lethal midline granuloma and should be taken into account (9, 12). Eye involvement in RP can be difficult to differentiate from other conditions like keratitis and scleritis, which may occur in rhumatoid arthritis, Wegener's granulomatosis, polyarteritis nodosa, Behçet's disease, and Cogan's disease (5-7, 11, 12).

Prevalence

In Rochester (Minnesota), the estimated annual incidence rate was 3.5/million. The peak age for disease onset is the fifth decade, although cases have been reported at both extremes of life (5). Most cases occur in whites. Both pediatric and elderly cases have been described with an age range of 6 to 87 years. Pregnancy does not seem to influence the disease course and the majority of pregnancies were successful (13). RP was reported to occur with equal frequency in both sexes. However, some authors found that the female/male ratio was about 3:1 (5) (Table 2).

Table 2. Clinical features of patients with relapsing polychondritis in 4 large series

	Mc Adam (6) [1976]	Michet (7) [1986]	Zeuner (10) [1997]	Trentham (5) [1998]
Variables: total number of patients followed up	N= 159	N= 112	N= 62	N= 66
Mean age at diagnosis (years)	44	51	47	46
Female/male	1/1	1/1	1.8/1	3/1
Mean duration of follow up (years)	-	6	-	8
Ear involvement (%)				
auricular chondritis	27	40	93.5	92
auditory dysfunction	7	9	19	7
vestibular dysfunction	-	4	23	6
Polyarthritis (%)	24	37	53	48
Nasal chondritis (%)	14	25	56.5	33
Ocular inflammation (%)	15	20	50	25
Respiratory tract inflammation (%)	15	26	31	39
Cardiovascular inflammation (%)	9	1	23	1

Skin involvement (%)	17	7	-	0.5
Kidney disease (%)	-	-	6.5	-
Nervous system involvement (%)	-	-	10	-

Clinical description
Associated diseases
In about one third of patients, RP is associated with vasculitis and autoimmune rheumatic diseases (Table 3) (14). The most commonly reported types of vasculitis range from isolated cutaneous leucocytoclastic vasculitis to systemic polyangiitis. Vessels of all sizes may be affected and large-vessel vasculitis is a well-recognized and potentially fatal complication. The MAGIC syndrome (mouth and genital ulcers with inflamed cartilage) has also been reported to be associated with RP (5). The second most commonly associated disorder is autoimmune rheumatic diseases mainly rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (5). Other disorders associated with RP are hematological malignant diseases, gastrointestinal disorders, endocrine diseases and others (Table 3).

Table 3. Conditions associated with relapsing polychondritis

Vasculitis	Hematological diseases
Leucocytoclastic	Myelodysplastic syndromes
Wegener's granulomatosis	Hodgkin's disease
Polyarteritis nodosa	Non Hodgkin's lymphoma
Churg-Strauss	Acute lymphoblastic
MAGIC syndrome	leukemia
Behçet's disease	Pernicious anemia
Mixed cryoglobulinemia	
	Endocrine disorders
	Diabetes mellitus type I
Autoimmune rheumatic diseases	Hashimoto thyroiditis
Rheumatoid arthritis	Graves disease
Systemic lupus erythematosus	Hypothyroidism
Sjögren's syndrome	
Mixed connective tissue disease	**Dermatological disorders**
	Psoriasis
	Pyoderma gangrenosum
	Vitiligo
	Panniculitis
Seronegative spondylarthophathies	Atopic dermatitis
Ankylosing spondylitis	Lichen planus
Psoriatic arthritis	
Reiter's syndrome	**Other diseases**
Gastrointestinal diseases	Myasthenia gravis
Crohn's disease	Familiar mediterranian fever
Ulcerative colitis	Thymoma
Primary biliary cirrhosis	
Retroperitonial fibrosis	

Clinical features
The demographic and clinical features of patients with RP are summarized in 4 large series in table 2. Disease onset is generally sudden and often flagrant. ***External ear involvement*** is the presenting symptom in almost all patients. RP typically attacks the cartilaginous portion of the pinna, sparing the lobe which lacks cartilage. Auricular chondritis presents with pain, redness or violaceous discoloration, swelling and tenderness involving one or both ears. Episodes can last a few days or weeks and patients recover from these episodes with or without treatment. After recurrent or persistent inflammation, the disease ends in cartilage destruction. The pinna loses its firmness, becomes soft and flops over or has a knobby or cauliflower appearance (5-8, 10-12). Hearing impairment may accompany ear involvement. This is due to closure of the external auditory meatus, serous otitis media and Eustachian tube obstruction. In addition, inflammation of the middle ear with sensorineural hearing loss and vestibular dysfunction with dizziness, ataxia, nausea and vomiting may also occur. In table 2, the main clinical features are presented from four large series (5-7, 10-12).

The second most common clinical finding of RP is joint pain with or without arthritis. All synovial joints may be affected. The most commonly involved joints are metacarpophalangeal, proximal interphalangeal joints, wrists and knees mimicking RA. Mono or oligoarthritis involving peripheral large joints also occur. Arthritis is non-deforming and non-erosive. Tests for rheumatoid factor are negative in affected patients (5-8, 10).

Involvement of the nasal cartilage may present with nasal pain, redness and swelling. Repeated attacks may cause destruction of the nasal bridge creating the characteristic "saddle-nose" deformity (5-7, 10, 12,15).

Ocular manifestations, occur in approximately 60% of reported patients with RP. The most common are scleritis, episcleritis, keratitis and conjuctivitis, which may occur early. Recurrences and exacerbations are very common. Scleritis and episcleritis usually parallel inflammation elsewhere, most commonly of the nose and joints (16). Uveitis occurs in about 25% of RP patients and 15 most often either an anterior uveitis or a sclerouveitis (16). Additional ocular manifestations include proptosis, corneal perforation, retinal vasculitis and optic neuritis leading to blindness (5-7, 13,16).

Respiratory symptoms are common and can be lethal. At disease onset, approximately 25% of the patients present with respiratory symptoms, while during disease course, this precentage increases to 50%. Inflammation occurs in the laryngeal, tracheal and bronchial cartilages which is accompanied by complaints

of hoarseness, non productive cough, dyspnea, wheezing and inspiratory stridor (5-8, 12,15). Early in the disease, patients may have tenderness over the thyroid cartilage and trachea. Involvement of laryngeal and epiglottal cartilage may lead to upper airway collapse, which may require emergency tracheostomy. Strictures usually appear in the subglottic region, causing increased susceptibility to secondary infections. Mortality from respiratory complications varies from 10 to 50%.

Cardiovascular involvement, although uncommon, is the second most frequent cause of death in patients with RP. Aortic regurgitation and mitral regurgitation occur in about 2 to 6% of the patients. Aortic regurgitation is more often attributable to progressive dilation of the aortic root of the ascending aorta than to inflammation of the valve leaflets. Rarely, dilation of the annulus of both mitral and tricuspid valves may cause mitral and tricuspid regurgitation (5-8, 17). Other manifestations include thoracic and abdominal aneurysm, myocarditis, pericarditis, silent myocardial infection, paroxysmal atrial tachycardia, and first-degree or even complete heart block.

Renal involvement can occur in RP in the absence of other associated diseases such as SLE or systemic vasculitis. Although rare, renal disease indicates worse prognosis. The most common histopathologic finding is mild mesangial proliferation, followed by focal and segmental necrotizing glomerulonephritis with crescents. Other abnormalities include glomerulosclerosis, IgA nephropathy and tubulointertitial nephritis. Immunofluorescence studies most often reveal faint deposits of C3, IgG or IgM primarily in the mesangium (5, 15).

Neurological abnormalities, not due to infection, rarely occur in patients with RP. The most common manifestations are cranial nerve palsies, cerebral aneurysms and aseptic meningitis (5-8). The pathogenesis of these symptoms is presumed to be vasculitis, but definite central nervous system vasculitis is rarely documented. Magnetic resonance imaging of the brain may show multifocal areas of enhancement consistent with cerebral vasculitis (11, 12).

Skin **manifestations,** RP causes many non-specific skin disorders, which may proceed the disease onset (chondritis) by 10 days to 20 years. Dermatologic symptoms are present in 50% of patients with RP. The frequency of skin involvement in the absence of an associated disease is about 35% but doubles in the presence of another systemic illness. In a recent study of 200 cases of RP, oral aphthous ulcers were the most frequent manifestation, followed

by nodules on the limbs with an erythema nodosum appearance (19). Other skin manifestations included: purpura, sterile pustules, superficial phlebitis and livedo reticularis. Limb ulcerations, urticarial papules, bluish red papules, distal necrosis and erythema elevatum diutinum were seen less frequently (19). Biopsy specimens often show leucocytoclastic, nercotizing or even granulomatosus vasculitis (5,19).

Additional symptoms, such as fatigue and weight loss, are common in RP and fever frequently accompanies acute flares (5).

Laboratory findings

During acute flares, patients may present with markers of inflammation, such as elevated erythrocyte sedimentation rate, and C-reactive protein, anemia, leucocytosis and thrombocytosis. Serum antibodies to collagen II have been found in about 40% to 50% of the patients with RP (20). Urinary glycosaminoglycans levels may be elevated. Recently, a serum 148-kDa noncollageneous cartilage matrix protein has been identified in patients with RP and RA. In patients with RP, tests for rheumatoid factor, antinuclear antibodies or antineutrophil cytoplasmic antibodies are negative, unless an associated autoimmune disease occurs. Conventional radiographs and computed tomography identified laryngotracheal lesions and thin section computed tomography defines abnormalities in lobar and segmental bronchi. Three-dimensional or spiral magnetic resonance imaging may provide better resolution. Pulmonary function tests are useful tools for monitoring changes over time. Finally, biopsy from ear cartilage or other inflamed areas may be useful to confirm the diagnosis.

Prognosis

Relapsing polychondritis is generally a progressive disease. The majority of the patients experience intermittent or fluctuant inflammatory manifestations. Many have persistent symptoms between acute flares. Most of them develop some degree of disability over the time. It includes bilateral deafness, impaired vision, phonation difficulties and respiratory problems. In 1986, the overall survival rates were 74% at 5 years and 55% at 10 years. However, recent studies showed a better outcome with a survival rate of 94% at 8-year follow-up (5-8). Pneumonia is the most common cause of death related to RP. These cases are often associated with airway stricture and long-term steroid use. Other causes of death include respiratory failure from airway collapse or obstruction and complications

of valvular heart disease and vasculitis (5-8, 10-12).

Management

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 (1 mg/kg/day) or even intravenous pulse methyl-prednisone in doses of 1 g/day (5-8, 10-12). The doses are then tapered to the lowest amounts that can prevent relapses. Whether steroid therapy should be continued during clinical remission periods remains unclear. Several immunosuppressive drugs have been used in patients who developed resistance to steroids and in patients who benefit from steroid sparing regimens. Azathioprine, cyclosporine-A and plasmapheresis have all been used as adjunctive therapies. Methotrexate has been an efficacious and well-tolerated steroid sparing medication. Trentham *et al.* reported 23 out of 31 patients receiving methotrexate, at an average dose of 17.5 mg/week, responded very well and were able to taper their prednisone dose from 19 mg/day to 5 mg/day (5). Dapsone (50 to 200 mg/day) has been advocated as an effective therapy for patients without cardiopulmonary involvement (5). Other approaches include the use of D-penicillamine, colchicine or even combination therapy such as dapsone and steroids, methotrexate, steroids and cyclosporine-A.

In patients with signs and features of systemic vasculitis, cyclophosphamide may be useful. More recently, anti-CD4 monoclonal antibody was reported to be effective in two patients with RP. Oral minocycline, as used for treating RA, was associated with improvement in a patient who had developed methotrexate toxicity (5).

A recent report describes a child successfully treated with daily oral fetal bovine type II collagen. Although, this is only a case report, the favorable safety profile of oral type II collagen makes it deserving of further study (21). Several biological therapies have been tried in RP. An anti-CD4 chimeric monoclonal antibody has been successful as a salvage therapy. Infliximab has been reported to induce remission in some cases (22). When other treatments fail, autologous stem cell transplantation may induce remission in RP patients (11, 12).

Patients who develop cardiorespiratory complications despite medical therapy may require surgery. Tracheostomy or stenting may be required to alleviate localized or extensive trancheobronchial disease. In addition, more

than 30% of the patients with valvular regurgitation need valve replacement (5).

Etiology

The cause of RP remains unknown. Specimens of inflamed cartilage may show distinctive features. There is a loss of basophilic staining of the cartilage matrix accompanied by perichondral inflammation of the cartilage. Perivascular mononuclear and polymorphonuclear cell infiltrates are present. The chondrocytes become vacuolated and necrotic and are eventually replaced by fibrous tissue (23).

Experimental studies in rabbits have shown that the intravenous injection of papain causes collapse of the external ear within a few hours. In addition, cartilage tissue shows loss of metachromatic staining without inflammation. In humans, cartilage destruction results from the release of degradative enzymes, including matrix metalloproteinases and reactive oxygen metabolites from inflammatory cells, chondrocytes and other cellular elements. The release of these enzymes is likely to be secondary to immune mediated activation of chondrocytes and other inflammatory cells by cytokines including interleukin-1 (IL-1)and tumor necrosis factor alpha (TNF-a). Pathogenesis of RP is unknown. However, autoimmunity is involved in several ways:

1) Tissue inflammation is composed of macrophages, CD4+ lymphocytes and B cells. In addition, deposition of immunoglobulins and complement components are found in tissue lesions of patients with RP.

2) Antibodies to type II collagen, as well as type IX and XI collagen are found in the sera of patients with RP (20). T cell clones isolated from a patient with RP were found to be specific for type II collagen peptide 261-273 (24).

3) Immunization of rodents with collagen II and immunization of rats with cartilage matrix protein (matrillin-1) results in the development of auricular chondritis and tracheal cartilage inflammation respectively (25-27).

4) Association with autoimmune diseases and HLA class II molecules (DR4) have been reported.

5) The tissue specificity of RP suggests that antigens derived from cartilage play an important role in driving and propagating the disease. Thus the following hypothesis may emerge.

In a genetically predisposed individual, an unknown x factor may cause immunological response to tissues rich in type II collagen and matrillin-1 (25-27). This leads to an inflammatory process of the cartilage, which causes cytokine and autoantibody production and immune

response perpetuation. This may cause chondrocyte damage, release of proteolytic enzymes, cartilage destruction and disease expression.

Genetic findings
Recent studies revealed significant association of RP with HLA-DR4 antigen. There was no predominance of any of the DRB1*04 subtype alleles in these patients (10). Additionally, no HLA-DR1 association was found. This contrasts with RA, where clear association with DRB1-*0401 and DRB1*0404 has been established. Therefore, the shared epitope hypothesis, as postulated for RA, is not likely to be true for RP.

Diagnostic methods
No specific diagnostic tools are required for the diagnosis of RP. Serum autoantibodies to collagen II and to 148-kDa noncollageneous cartilage matrix protein may be helpful. Chest conventional radiographs, pulmonary function test and chest CT tomography may be useful for diagnosis. Finally, cartilage biopsy from ear or other inflamed tissues may be useful to confirm the diagnosis.

Genetic counseling
Genetic counseling is not available.

Unresolved questions
Origin of the unknown etiological factor.
Role of collagen II and matrillin-1 in disease pathogenesis.
Perpetuation and activation of the immune system.

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