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Relapsing Polychondritis

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Abstract Relapsing polychondritis (RP) is a systemic autoimmune disorder characterized by episodic and progressive inflammatory disease most commonly presenting as inflammation of the cartilage of the ears, nose, tracheobronchial tree and joints. The course of RP varies from a low-grade, mild condition up to a fulminating and rapidly progressive disease. Spontaneous remissions are common.

This chapter also summarizes important aspects of the disease with a focus on diagnostics criteria. In fact, over the years, three sets of diagnostic criteria for RP have been proposed by McAdam, Damiani and Levine, and Michet, respectively. Although these criteria have not been re-examined by consensus group members and despite the lack of validation, these show high affordability in discriminating patients affected by RP in every day clinical practice.

In conclusion, for achieving reliable classification criteria that would also be useful for the diagnosis of RP, more extensive multicenter studies are needed.

Keywords Relapsing Polychondritis · classification criteria · diagnosis

Relapsing Polychondritis

Relapsing polychondritis (RP) is an episodic and progressive inflammatory disease most commonly presenting as inflammation of the cartilage of the ears, nose, tracheobronchial tree and joints.

Epidemiology

RP is most commonly reported in whites, begins between the age of 20 and 60 years, with a peak in the 40 s. The annual incidence has been estimated as 3.5 cases per million (1). The male-to-female ratio appears to be equal in some series of cases, but Trentham reported a ratio of 3:1 (2).

History

In 1923, Kaksch-Wartenhorst described the first clinical picture of RP as "polychondropathia" (3). The disease also has been called chondromalacia, diffuse perichondritis, chronic atrophic polychondritis, diffuse chondrolysis and dyschondroplasia. The term *relapsing polychondritis* was first introduced in 1960 by Pearson et al., who described a rare condition characterized by *relapsing* inflammatory disease of cartilagineous structures (4).

Pathogenesis

Although the etiology of RP remains unknown, the pathogenesis seems to be an immunologic reaction to type II collagen present in the cartilage and in the sclera of the eye. Patients with RP have demonstrated both autoantibodies and cellular immune reaction to type II, IX and XI collagen. Immunofluorescence studies of affected cartilage have shown granule deposits of immunoglobulin and complement, suggesting the presence of immune complexes. Most recently, an increase in HLA-DR4 antigen was detected in patients with RP, suggesting a genetic predisposition for the disease (5, 6).

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TABLE 9.1. Clinical features of relapsing polychondritis (7).

Feature	Presenting (%)	Cumulative (%)
Auricular chondritis	43	89
Arthritis	32	72
Nasal chondritis	21	61
Ocular inflammation	18	59
Layngotraceal symptoms	23	55
Reduced hearing	7	40
Vestibular dysfunction	4	28 no study by McAdam
Microhematuria	15	26 only study by Michet
Saddle nose deformity	11	25 no study by McAdam
Cutaneous	4	25 no study by McAdam
Laryngotracheal stricture	15	23 only study by Michet
Vasculitis	2	14 no study by McAdam
Elevated creatinine	7	13 only study by Michet
Aortic or mitral regurgitation	0	12 no study by McAdam
Aneurysm	0	4 only study by Michet

Data derived from three large case series and reviews (2: *n 66*; 10: *n 112*; 11: *n 159* = 337 patients).

Clinical Manifestations

The clinical features of RP are illustrated in Table 9.1 (7).

– Auricular chondritis and arthritis are the most common presenting signs, characterized respectively by the pain, swelling, redness of the cartilaginous portion of the external ear and oligo or polyarthritis. The arthritis is intermittent, migratory, asymmetric, seronegative and generally nonerosive.

Conductive hearing loss can result from stenosis of the auditory canal, otitis media or Eustachian tube chondritis. Sudden onset of vertigo and hearing loss may occur owing to involvement of the vasculitis of the auditory artery. Chondritis of nasal cartilage, laryngeal and tracheobronchial tract may result in collapse nasal cartilage (saddle nose deformity), choking sensation, cough, stridor, respiratory obstruction with high morbidity and mortality. Secondary infections of the respiratory tract are also common in patients with severe airway involvement.

– Ocular inflammation occurs in 60% of patients. Common presentations are scleritis, episcleritis, conjunctivitis, iritis, keratitis, optic neuritis, retinopathy and corneal melt. Less common are orbital pseudotumor, extraocular muscle palsy and lid edema.
– Dermatologic involvement is frequent during the course of the disease. Oral ulcers are the most commonly mucocutaneous lesion, followed by erythema nodosum, purpura, pustules, superficial phlebitis, livedo reticularis and limb ulcerations.
– Cardiovascular involvement in RP includes aortites, pericarditis, aortic and mitral regurgitation, cardiac ischemia and complete heart block. Vascular involvement of large vessels may present as thoracic and abdominal aneurysm, thrombophlebitis and arterial thrombosis due to vasculitis or coagulopathy.
– Renal involvement in RP is not frequent and includes mesangial expansion, IgA nephropathy, tubulointerstitial nephritis and segmental necrotizing crescentic glomerulonephritis (2, 8, 9,10, 11).
– Neurologic manifestations in RP occur in approximately 3% of patients and most commonly involve cranial nerves II, III, IV, VI, VII and VIII. Cerebral vasculitis, headaches, cerebral aneurism, thromboencephalitis, confusion and seizures have been also described.
– Associated disorders: More than 30% of patients with RP have a rheumatological or hematological disease such as systemic lupus erythematosus, rheumatoid arthritis, systemic sclerosis, Sjögren syndrome, Behçet's disease, Wegener's granulomatosis, Churg–Strauss syndrome, cryoglobulinemia, dysmyelopoietic syndrome, Hodgkins and non-Hodgkins lymphoma and chronic myelomonocytic leukaemia. In most cases, the associated disorders precede the onset of RP by several months or years. Because of the myriad of disease associations, it has been proposed that the RP be thought of as a syndrome, which can be primary or secondary (10, 12, 13, 14, 15).

Biochemical Features

The laboratory tests are nonspecific and helpful only when they serve to exclude other conditions or associated disorders to RP. The findings are only an elevated erythrocyte sedimentation rate during active disease, moderate leukocytosis and mild anemia typical of chronic disease. Antibodies to collagen types II, IX and XI can be detected in one-third of patients, but such antibodies can be found in other rheumatologic conditions and have limited diagnostic value because of relatively low specificity. Anti-collagen type II antibodies are found in the acute phase of RP, and

their serum levels seem to correlate with disease severity (5), but Trentham reports that this antibody does not correlate with disease activity or severity (2).

Occasionally, patients may have positive antinuclear antibodies (ANAs), rheumatoid factor, anti-native DNA, anti-neutrophil cytoplasm antibodies, and cryoglobulins, but these patients may have overlaps with other autoimmune disease.

Pathological Features

No biopsy finding is pathognomonic for RP; therefore, biopsy is not necessary because the diagnosis is based on clinical features. Histologically, RP is characterized by perichondrial inflammation that involves mainly lymphocytes, but neutrophils may be predominant in early lesions. Granulation tissue or fibrosis, and calcification or ossification may be found (8). Immunoflorescence studies may show the presence of immunoglobulins and C3 deposits along the chondrofibrous junction and in perichondral vessel walls.

Diagnostic Criteria

Diagnostic criteria (Table 9.2) for RP were described by McAdam et al. in 1976 (8), Damiani and Levine in 1979 (16), and Michet et al. in 1986 (9). These three sets of criteria are currently used by several authors for the diagnosis of RP because they are considered complementary to each other instead of antithetic.

The diagnostic criteria of McAdam et al. require at least three of the six following criteria: bilateral auricular chondritis, nonerosive inflammatory polyarthritis, nasal chondritis, ocular inflammation, respiratory tract chondritis, and cochlear or vestibular dysfunction.

Biopsy is not necessary in the presence of a typical clinical presentation. If the clinical presentation is uncertain, histological examination can exclude other causes of chondritis, such as bacterial infections, syphilis, leprosy, fungal invasion and overlap vasculitis.

The diagnostic criteria of Damiani and Levine require only one of following three criteria:

- at least three of McAdam's criteria with nonhistological confirmation
- one or more of McAdam's criteria with histological confirmation
- chondritis in two or more separate anatomical locations with response to steroids and/or dapsone.

The diagnostic criteria of Michet et al. require only one of following two criteria:

- inflammatory episodes involving at least two of these sites: auricular, nasal and laryngotracheal cartilages
- one of the earlier mentioned sites and two other manifestations, including ocular inflammation, hearing loss, vestibular dysfunction or seronegative inflammatory arthritis. These criteria overlap with the prior.

Criticism on the Diagnostics Criteria

The three sets of criteria mentioned earlier are useful for diagnostic purposes, but they have never been officially validated mainly for four reasons:

1) these criteria have been empirically defined on the basis of the personal experience of each author without a larger international consensus of experts;
2) the three studies lack a control group; this is not methodologically correct and does not even allow to build a classification tree or to perform a statistical analysis for the validation of classification criteria;
3) specificity, sensitivity, diagnostic accuracy and positive and negative predictive values have never been calculated for the absence of adequate control groups.

TABLE 9.2. Diagnostic criteria for relapsing polychondritis.

Author	Criteria	Required	Total
McAdam et al. (8)	1) Recurrent chondritis of both auricles 2) Nonerosive inflammatory polyarthritis 3) Chondritis of nasal cartilage 4) Inflammation of ocular structures including conjunctivitis, keratitis, scleritis/episcleritis and uveitis 5) Chondritis of the respiratory tract involving laryngeal and tracheal cartilages 6) Cochlear or vestibular damage manifested by neurosensory hearing loss, tinnitus and vertigo.	3	6
Damiani and Levine (16)	1) At least three of McAdam's criteria 2) One or more of McAdam's criteria and positive histology. 3) Chondritis in two or more separate anatomical locations with response to steroids and/or dapsone.	1	3
Michet et al. (9)	1) Inflammatory episodes involving at least two of three sites: auricular, nasal or laryngotracheal cartilage 2) One of those sites and two other manifestations, including ocular inflammation, vestibular dysfunction, seronegative arthritis and hearing loss	1	2

Furthermore, the lack of controls does not even allow an "a posteriori" statistical evaluation of these parameters;

4) the criteria proposed by Damiani and Michet are substantially based on those elaborated by McAdam; therefore they have a selection bias determined by both a single author's experience and, again, a lack of control group.

Nevertheless, despite the lack of validation, these criteria show high affordability in discriminating patients affected by RP. In fact, some of criteria such as auricular chondritis, saddle nose deformity and laryngeal chondritis are very frequent in RP while they are absent or not so frequent in other conditions. In fact RP shares several signs and symptoms with other systemic diseases that should be considered in differential diagnosis. Diseases that must be considered in the differential diagnosis include polyarterite nodosa, Cogan's syndrome, Behçet's disease, sarcoidosis, rheumatoid arthritis and Takayasu syndrome where auricular, nasal and laringeal chondritis have never been reported. In any case, and especially in controversial cases, cartilage biopsy has been demonstrated to be a determinant for the differential diagnosis with other forms of chondritis, including infection chondritis sustained by leprosy, Syphilis, Streptococcus, Pseudomonas, traumatic chondritis, neoplastic chondritis such as natural Killer lymphoma and various malignancies and vasculitis chondritis which include those seen in Wegener's granulomatosis where saddle nose deformity is frequent.

Prognosis

The course of RP varies from a low-grade, mild condition up to fulminating and rapidly progressive disease. Spontaneous remissions are common. The survival rate is 74% at 5 years and 55% at 10 years in the study of Michet, but Trentham in 1988 reported a 94% survival rate and average disease duration of 8 years. Common causes of death are pulmonary infection, airway collapse, systemic vasculitis and glomerulonephrits. Factors predictive of the severity of the disease and fatalities are anemia, saddle nose deformity, vasculitis, arthritis, laryngotracheal strictures and hematuria at the time of diagnosis (2, 9).

Therapy

A standardized therapeutic protocol for RP has not been established because the disease is rare.

Nonsteroidal anti-inflammatory drugs, dapsone and/or colchicine have been used in mild polychondritis limited to arthralgia and nasal or auricular chondritis with benefits. Dapsone is often first used for the systemic manifestations of RP in some patients, but 9 of 14 patients in other series did not respond to this drug (2, 8).

Corticosteroids continue to be a mainstay of medical management of RP and decrease the frequency and severity of attacks. Traditional therapy is 10–20 mg/day of prednisone for mild to moderate auricular and nasal chondritis or arthritis. Doses of prednisone 0.75 to 1 mg/kg of body weight per day or pulse methylprednisolone (1 g/day for 3 days) and/or an immunosuppressive agent (azathioprine, cyclophosphamide, methotrexate or cyclosporine) should be initiated in patients with more severe disease, such as acute airway obstruction and cardiovascular and renal involvement.

Other therapies reported in refractory cases are plasmapheresis, anti-CD4 monoclonal antibodies and autologous stem-cell transplantation.

Intravenous infusions of infliximab have been used in resistant RP with good response.

Surgical intervention is indicated for certain respiratory and cardiovascular complications (2, 17, 18, 19).

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