


Glossary

Axon reflex – activation of a sensory receptor results in orthodromic conduction of the action potential toward the central nervous system, and antidromic conduction along peripheral branches of the axon. The action potential can produce release of neuroactive agents from retrogradely invaded terminals

Breuer–Hering reflex (B–H) – reflex changes in breathing pattern elicited by activation of SAR. Activation during inspiration shortens inspiratory duration and reduces tidal volume. Activation by maintained inflation during expiration results in expiratory prolongation

Functional residual capacity (FRC) – volume of air in the lungs at the end of a normal expiration

Non-adrenergic, non-cholinergic (NANC) – airway nerve fibers that release any of a variety of transmitter substances but do not release either noradrenaline or acetylcholine

Neuroepithelial bodies (NEBs) – collection of endocrine cells in airway epithelium that contain dense core vesicles and a variety of neuroactive substances. They are extensively innervated by vagal fibers and fibers arising in dorsal root ganglia. They are responsive to hypoxia but their physiological role requires clarification

Rapidly adapting pulmonary stretch receptor (RAR) – receptor in epithelium and subepithelial layers of airways with myelinated axon responsive to inhaled irritants, large lung inflation

Slowly adapting pulmonary stretch receptor (SAR) – receptor in airway smooth muscle with myelinated axon that is responsive to lung inflation

RELAPSING POLYCHONDRITIS

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Abstract

Relapsing polychondritis is a rare, chronic, episodic, and progressive inflammatory disease of unknown cause. It is characterized by inflammation and destruction of cartilaginous structures found in ears, nose, joints, and the tracheobronchial tree. Relapsing polychondritis can also affect other proteoglycan-rich structures, such as the eye, kidneys, heart, blood vessels, and inner ear, or cause systemic symptoms such as fever, lethargy, and weight loss. The exact etiology and pathogenesis of relapsing polychondritis remains unknown, but evidence suggest that it is an immunologically mediated disease. The most common manifestations include auricular and nasal chondritis, arthritis, episcleritis, and inflammation of cartilaginous tissues along the laryngotracheal tree. The correct diagnosis is usually delayed in most patients due to its rarity and its multiple clinical features. No exact data exist on the incidence, prevalence, and mortality of relapsing polychondritis. The most common natural course of relapsing polychondritis is fluctuating but progressive with episodic flare-ups of inflammation that can eventually lead to significant dysfunction of the involved organs. Corticosteroids have been shown to be the most effective treatment, but their side effects prevent any long-term therapy. Other immunosuppressing agents, such as dapsone, methotrexate, azathioprine, and cyclophosphamide, have also been used.

Introduction

Relapsing polychondritis is a rare, chronic, episodic, and progressive inflammatory disease in which different cartilaginous structures found in ears, nose,
joints, and the tracheobronchial tree are mainly affected. Relapsing polychondritis can also affect other proteoglycan-rich structures, such as the eye, kidneys, heart, blood vessels, and inner ear, or cause systemic symptoms such as fever, lethargy, and weight loss. The correct diagnosis is usually delayed in most patients due to its rarity and its multiple clinical features. No exact data exist on the incidence, prevalence, and mortality of relapsing polychondritis. The incidence in Rochester, Minnesota, is estimated to be 3.5 per 1 million population per year. The most common natural course of relapsing polychondritis is fluctuating but progressive with episodic flare-ups of inflammation that can eventually lead to significant dysfunction of the involved organs. Corticosteroids have been shown to be the most effective treatment, but their side effects prevent any long-term therapy. Other drugs, such as dapsone, methotrexate, azathioprine, and cyclophosphamide, have also been used.

**Etiology and Pathogenesis**

The exact etiology and pathogenesis of relapsing polychondritis remains unknown. The role of the immune system in the pathogenesis of relapsing polychondritis has been supported by different lines of evidence:

1. Serum autoantibodies against collagen type II (present in cartilage in large amounts), as well as types IX and XI, have been found in some patients with relapsing polychondritis.
2. Cell-mediated immune responses directed toward cartilage components have been demonstrated by some investigators.
3. Immunofluorescence studies of cartilage have shown granular IgG, IgA, IgM, and C3 deposits at the junction of fibrous and cartilaginous tissue, suggesting the presence of immune complexes.
4. An association with HLA-DR4 antigen has been reported more frequently in patients with relapsing polychondritis compared to controls.
5. Tissue infiltration composed of plasma cells, lymphocytes, and polymorphonuclear leukocytes has been well described.
6. The frequent association of relapsing polychondritis with other autoimmune diseases and the response to immunosuppressive agents support the theory of autoimmune pathogenesis.

**Pathology**

The initial pathologic change is a loss of basophilic staining, followed by cellular infiltrates of lymphocytes, plasma cells, and neutrophils at the chondrodermal junction in the affected cartilaginous sites. The lymphocytosis is a CD4 helper T cells dominate process. IgG and C3 may now be seen throughout the matrix. Finally, the chondrocytes become vacuolated and pyknotic, and they are replaced by fibroblastic granulation tissue that completely disrupts the tissue architecture. Focal regions of calcification and bone formation may be present. The ocular histopathology in patients with relapsing polychondritis includes mononuclear inflammatory cells, plasma cells, and even true vasculitis.

**Clinical Features**

Relapsing polychondritis usually develops between the ages of 40 and 60 years, but the disease has been described in almost all ages. Both genders are affected with the same frequency, but most cases involve white patients. Since relapsing polychondritis is uncommon and can affect multiple organs and systems at different times, there is usually a significant mean delay of 2.9 years until diagnosis is established. Relapsing polychondritis should be considered a syndrome that can be primary or secondary, depending on its association with other entities. Up to 37% of patients have an associated condition, such as a hematologic disorder, connective tissue disease, vasculitis, dermatologic disorder, or other autoimmune disorder (Table 1).

**Auricular Chondritis, Vestibular Dysfunction, and Nasal Chondritis**

Auricular chondritis is the most frequent presenting manifestation in patients with relapsing polychondritis. Patients present with external ear pain and redness and swelling of the cartilaginous portion of the ear with sparing of the lobule (Figure 1). The involvement of the external ear usually occurs in a relapsing pattern persisting for several weeks or resolving spontaneously after a few days. After several episodes or after a severe single one, the cartilaginous pinna becomes floppy or deformed. The external auditory canal and Eustachian tube are frequently involved also, with edema and collapse causing subsequent conductive hearing loss and otitis media. Sensorineural hearing loss with or without symptoms of vestibular dysfunction (dizziness, ataxia, nausea, and vomiting) can occur presumably from vasculitis in branches of the internal auditory artery. Nasal chondritis develops suddenly, is very painful, and the inflammation can destroy the distal part of the nasal cartilage leading to a saddle nose deformity (Figure 2).
Otorhinolaryngeal Manifestations

More than 50% of patients develop chondritis of the laryngotracheal cartilages and may present with anterior neck pain, cough, hoarseness, dyspnea, wheezing, or choking. Acute upper airway obstruction may develop due to inflammation and edema of the glottic, laryngeal, or subglottic area. Some patients may require an emergency tracheostomy even before there is an established diagnosis.

Pulmonary Manifestations

Involvement of the respiratory tract (trachea and first- to-second order bronchi) is the presenting feature in up to 26% of patients with relapsing polychondritis. Acute swelling of the tracheobronchial tree can lead to localized or diffuse obstruction of the airway tract. The damaged tracheal and bronchial rings may lose their rigidity and collapse, allowing the development of dynamic obstruction. Thus, pulmonary function tests with flow volume loops should be performed in all patients, even in those without respiratory symptoms. Spirometry shows obstructive ventilatory impairment with reduction in expiratory flow and maximal voluntary ventilation. Other findings seen in patients with relapsing polychondritis include tracheal/bronchial stenosis due to granulation tissue, calcification of the airway walls, and obstructive bronchiectasis.

Chest radiographic findings are usually not sensitive or specific but include pneumonia, atelectasis, calcifications in the airway wall, and prominence of...
the thoracic aorta. Computed tomography (CT) of the chest is more useful in revealing details of the tracheobronchial tree (e.g., narrowing of the lumen and calcifications or thickening of the tracheal/bronchial wall).

Bronchoscopic exam of the airway confirms the diagnosis, showing erythema, edema, deformation, and collapse of the tracheobronchial tree (Figure 3). In addition, biopsies of the cartilage can be obtained through bronchoscopy. It is important to remember that bronchoscopy is less accurate in evaluating the functional status of the airway compared to pulmonary function testing. Bronchoscopy may also precipitate further respiratory distress since it can induce trauma in an airway suffering active inflammation.

**Musculoskeletal Manifestations**

Arthritis is the second most common presenting symptom and is present in up to 85% of patients with relapsing polychondritis. When relapsing polychondritis is not associated with any other collagen vascular disease, the arthritis is nonerosive, asymmetric, seronegative, and can affect all synovial joints. Metacarpophalangeal, interphalangeal, and knee joints are the most commonly affected.

**Renal Manifestations**

Renal disease occurs in 10–22% of patients with relapsing polychondritis, especially in cases associated with vasculitis or other collagen vascular diseases. The most common renal pathology is mesangial proliferation, but other pathologies, such as IgA nephropathy, segmental necrotizing crescentic glomerulonephritis, and tubulointerstitial nephritis, have also been described.

**Cardiovascular Manifestations**

Aortic regurgitation is the most frequent form of cardiovascular involvement in relapsing polychondritis, occurring in approximately 4–10% of patients. Ascending aortitis extending to the valve ring is responsible for aortic regurgitation and explains the common association with aortic aneurysms. Other forms of cardiovascular involvement include abdominal aortic aneurysms, myocarditis, pericarditis, coronary vasculitis, impairment of the conduction system, thrombophlebitis, and arterial thrombosis. These thrombotic complications have been explained by the presence of vasculitis or an associated antiphospholipid syndrome.

**Dermatologic Manifestations**

Skin involvement in the absence of an associated condition occurs in approximately 35% of cases. The most common manifestations are oral aphthous ulcers, followed by macules, papules, nodules, and livedo reticularis. The most common histologic diagnosis in these lesions is leukocytoclastic vasculitis, with other histologic patterns including neutrophilic dermatosis, thrombotic occlusion of dermal vessels, and even granulomatous vasculitis. Patients with an associated myelodysplastic syndrome commonly have dermatologic involvement. Elderly patients with relapsing polychondritis and skin involvement should be monitored for the development of a myelodysplastic syndrome.

**Neurologic Manifestations**

Central and peripheral nervous system involvement occurs in only 3% of patients. The cranial nerves are most commonly affected, but seizures, headache, hemiplegia, encephalopathy, and cerebral aneurysms have been described.

**Ocular Manifestations**

Ocular disease occurs eventually in up to 60% of patients with relapsing polychondritis. Most of these patients tend to develop multiple systemic manifestations. Episcleritis and scleritis are the most common manifestations, usually in parallel with inflammation of the nose and joints (Figure 4). Other types of ocular involvement are uveitis, keratitis, keratoconjunctivitis sicca, central retinal vein occlusion, and ischemic optic neuropathy.
Diagnosis

Although relapsing polychondritis seems to be easy to diagnose when it presents with its most typical symptoms, the correct diagnosis in many cases is delayed due to its rarity and multiple possible presenting features. McAdam and co-workers were the first to propose diagnostic criteria using the most common clinical features, requiring at least three out of six features to confirm the diagnosis (Table 2). Michet and colleagues modified these diagnostic criteria, requiring chondritis in two of three sites (auricular, nasal, or laryngotracheal) or one of those sites and two other signs, including ocular inflammation, vestibular dysfunction, seronegative arthritis, and hearing loss. In most patients, it is not necessary to biopsy the affected cartilaginous sites.

No specific laboratory test exists for the diagnosis of relapsing polychondritis. During acute exacerbations, it is possible to observe elevated erythrocyte sedimentation rate, anemia of chronic disease, leukocytosis, thrombocytosis, and hypergammaglobulinemia.

Serum antibodies to type II collagen have been detected in 20–50% of patients. However, the use of these antibodies is limited due to a relatively low specificity. Other serologic tests, such as rheumatoid factor, antinuclear antibodies, antineutrophil cytoplasmic antibodies, and complement levels, are helpful if other associated conditions are present simultaneously. Other ancillary tests, such as urinalysis, creatinine, echocardiography, CT chest, pulmonary function tests, and skin biopsy, can be helpful to assess the organs and systems affected by the disease.

Some autoimmune disorders can overlap clinical features or involve multiple organs, as is the case for relapsing polychondritis. Wegener’s granulomatosis and polyarteritis nodosa can cause ocular inflammation, polyarthritis, and cochlear and vestibular symptoms. However, these two entities have not been reported to cause chondritis and usually affect the lung parenchyma, which is not seen in relapsing polychondritis.

Rheumatoid arthritis can also cause ocular inflammation, vasculitis, and multiple organ involvement. However, the joint involvement of rheumatoid arthritis is usually symmetric and erosive as opposed to the nonerosive arthritis seen in relapsing polychondritis. Vasculitis of medium and large vessels, such as the polyarteritis nodosa and Takayasu’s arthritis, may mimic the cardiovascular involvement seen in relapsing polychondritis with development of aneurysms or arteritis with or without thrombosis.

Management and Therapy

There is no standard medical therapy for relapsing polychondritis due to its rarity, wide variety of presentations, and unpredictable course. Therapeutic guidelines are based on reports of treatment success from small series of patients or isolated cases.

Arthritis or mild chondritis of nose and ears can be treated with the nonsteroidal anti-inflammatory drugs dapsone or colchicine. However, systemic corticosteroids are the traditional agents used in acute exacerbations. Prednisone at a high dose of 1 mg kg⁻¹ day⁻¹ is used for cases with ocular involvement, laryngeal inflammation, sensorineural hearing loss, vestibular symptoms, and vascular and renal involvement. Although steroids may resolve acute inflammation of the cartilage and decrease the frequency and

Table 2 Diagnostic criteria for relapsing polychondritis

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<th>McAdam et al. (1976) criteria</th>
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<tr>
<td>Bilateral auricular chondritis</td>
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<td>Nasal chondritis</td>
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<td>Nonerosive, seronegative inflammatory polyarthritis</td>
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<tr>
<td>Ocular inflammation (conjunctivitis, keratitis, scleritis and/or episcleritis, uveitis)</td>
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<tr>
<td>Respiratory tract chondritis (laryngeal and/or tracheal cartilage)</td>
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<tr>
<td>Cochlear and/or vestibular dysfunction (neurosensorial hearing loss, tinnitus, and vertigo)</td>
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<th>Michet et al. (1986) criteria</th>
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<tr>
<td>Proven inflammation in two of three cartilaginous sites: auricular, nasal, or laryngotracheal</td>
</tr>
<tr>
<td>Proven inflammation in one of three cartilaginous sites: auricular, nasal, or laryngotracheal; plus two other clinical signs, including ocular inflammation, vestibular dysfunction, seronegative arthritis, and hearing loss</td>
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a Three criteria are the minimum required to confirm the diagnosis.
b One diagnostic criteria is enough to confirm the diagnosis.
degree of the exacerbations, they have no effect on the overall progression of the disease and do not alter the risk of multisystem organ involvement or the structural damage to cartilaginous organs. When an acute exacerbation goes into remission, the high doses of steroids can be gradually tapered to moderate maintenance doses. In patients with chronic active inflammation that requires high-dose steroids, the use of methotrexate or azathioprine may allow a reduction of the corticosteroid dose.

In cases of severe end-organ damage, such as ocular, pulmonary, cardiac, or renal involvement, pulses of oral or intravenous cyclophosphamide can be used. Cyclosporine A has also been used with success in refractory cases to other agents. Infliximab has been tried in resistant relapsing polychondritis and associated scleritis.

The respiratory problems caused by relapsing polychondritis can present suddenly and become very difficult to manage. Adliff and colleagues reported the use of nasal CPAP as a pneumatic splint for the tracheobronchial tree, preventing airway collapse and obtaining temporary control of airway patency. For sudden and severe upper airway obstruction, a tracheostomy can be life-saving. Despite a significant risk, endotracheal intubation may be needed, preferably with a small endotracheal tube because of the reduced glottic diameter. Airway stents, montgomery T tubes, and self-expanding metallic stents have been used in patients with collapse or refractory stenosis of the airway. They are able to gain airway patency but are associated with many potential problems, including erosion of the stent through the trachea, sudden asphyxia from stent displacement, aspiration pneumonia, development of granulation tissue or mucosal ulceration, and retention of airway secretions.

Most patients with relapsing polychondritis have a fluctuating but slowly progressive course with unpredictable severity and site of involvement by the inflammatory process. In a 6-year follow-up study from the Mayo Clinic, 86% of patients were reported to have intermittent manifestations with a median of five episodes. The majority of patients develop some disability, depending on the organs involved and the severity of the disease (deafness, impaired vision, speech problems, and cardiopulmonary problems).

In terms of mortality, Trentham and co-workers in 1998 reported a 94% survival rate with an average disease duration of 8 years. This number represents an improvement compared to the 55% survival rate at 10 years reported by McAdam et al. in 1976. The improved survival has been explained by improved medical and surgical management of the respiratory and cardiovascular complications. The most common causes of death are infections, vasculitis, and malignancies. Pulmonary infections are of particular importance. They are severe and complicated due to the use of corticosteroid therapy and airway stricture/collapse, which impair the defense and clearing mechanisms of the lung.


Further Reading