Relapsing Polychondritis: An Analysis of 11 Patients

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Objective: To analyze 11 patients with relapsing polychondritis reported by 3 hospitals in our country.

Patients and method: We describe 11 cases of relapsing polychondritis reported by 3 hospitals in our country, analyzing gender, age at the beginning of the disease, delay time in diagnosis, clinical manifestations at the beginning of the disease, and during follow-up, initial treatment, and treatment in the “chronic phase” of the disease.

Results: We described 8 female patients and 4 males, with a mean age of 40.8 years. The delay time in diagnosis was from 4 months to 4 years. The main manifestations were: auricular chondritis in 8 patients (72.7%), hearing loss in 4 (36.3%), and dysphonia in 4 (36.3%). The complications included subglotic stenosis in 4 patients (36.3%), episcleritis in 2 (18.1%), 1 retinal and corneal detachment with macular lesion (9%), conductive and sensorial hearing loss in 2 (18.1%), glomerulonephritis in 2 (18.1%), and mitral and tricuspid insufficiency in 1 patient (9.0%). All of them received prednisone. Cyclophosphamide, methotrexate, and azathioprine were the most common immunosuppressants used.

Conclusions: This is the largest cohort reported in our country, sharing clinical and outcome patterns reported in other series and in the literature. Response to steroids is good; however, we need to consider other therapeutic options because the disease continues progressing and relapsing.

Key words: Relapsing polychondritis. Cartilage. Clinical manifestations. Therapeutics.

Relapsing polychondritis (RP) is a rare multisystemic disease, characterized by episodic and progressive inflammation of cartilage structures such as the elastic cartilage of the ears and nose, the hyaline cartilage of the peripheral joints, fibrocartilage of the axial skeleton, and...
cartilage of the tracheobronchial tree, as well as other structures that have a rich content of proteoglycans such as eyes, heart, blood vessels, and kidneys.1-3 The annual incidence is 3.5 cases per million,4,5 with an average age at diagnosis of 47 years6,4 and a female: male ratio of 1:3:1.1,2 Its etiology is unknown; however, among other findings circulating autoantibodies directed against type II collagen have been described, in proportions ranging from 33%5-7 to 60% of cases,8 as well as antibodies against type IX and XI collagen.1,4,10 IgG, IgM and IgA, and C3 immunocomplex deposit has also been described.1,2 Recent evidence points to an immune response to non-collagen proteins such as matrilin-1, as well as oligomeric proteins from the cartilage matrix.9-12 An increase in HLA DR4 without a predominant subtype has also been described.1,2,4,10,11 Because its etiology is unknown, there is no established therapy. Steroids have been effective in suppressing activity and in reducing the frequency and severity of relapses1-4; however, in some cases it is necessary to use immunsuppressants such as cyclophosphamide, azathioprine, methotrexate,1,4,13-19 and cyclosporin A.3,4,18,20 Other treatments that have been employed for cases that are refractory to previously mentioned medications include colchicine4,21 and dapsone22,23, biologic therapy with anti-CD4,4,18 and against tumor necrosis factor alpha have been recently used, obtaining good responses; nonetheless, infections, occasionally serious, have been the most frequent adverse event present, making it necessary to carefully ponder their administration to immunodeficient patients.4,24,25 Complete remission after autologous stem-cell transplant has been reported, and Navarro et al have described an adequate response with the use of daily, oral bovine type II collagen.4 Because of the respiratory compromise present in these patients, some require permanent tracheotomy, the installation of bronchial or tracheal stents and mechanic ventilation with continuous positive pressure.26-28 Its course can be lethal, in 50% of cases due to dyspnea that arises after collapse of the respiratory airways, recurrent pneumonia, and other renal and cardiovascular complications; as well as vasculitis, which can also lead to a very poor prognosis.1,2,4,17 In this study we analyze the epidemiologic, clinical, and therapeutic aspects in a series of patients from 3 rheumatology centers.

**Patients and Methods**

We describe 11 cases of RP, 4 from the Hospital Juárez de México (SS), 3 from Centro Médico Nacional 20 de Noviembre (ISSSTE), and 4 from Hospital General de México (SS). Analyzed aspects include determination of gender, age at onset, time since onset to diagnosis of the disease, initial clinical findings, and findings during follow-up, initial treatment as well as the therapeutics employed in the chronic phase of illness.

**Results**

Eleven cases of RP are described, 8 women and 3 men. Mean age at onset of disease was 40.8 years (Figure 1). Time since onset of disease at the moment of the diagnosis was 4 months to 4 years (Figure 2). Among the clinical manifestations the following stand out: ear chondritis (Figure 3) in 8 (72.7%) cases, hearing cartilage of the tracheobronchial tree, as well as other structures that have a rich content of proteoglycans such as eyes, heart, blood vessels, and kidneys.1-3 The annual incidence is 3.5 cases per million,4,5 with an average age at diagnosis of 47 years6,4 and a female: male ratio of 1:3:1.1,2 Its etiology is unknown; however, among other findings circulating autoantibodies directed against type II collagen have been described, in proportions ranging from 33%5-7 to 60% of cases,8 as well as antibodies against type IX and XI collagen.1,4,10 IgG, IgM and IgA, and C3 immunocomplex deposit has also been described.1,2 Recent evidence points to an immune response to non-collagen proteins such as matrilin-1, as well as oligomeric proteins from the cartilage matrix.9-12 An increase in HLA DR4 without a predominant subtype has also been described.1,2,4,10,11 Because its etiology is unknown, there is no established therapy. Steroids have been effective in suppressing activity and in reducing the frequency and severity of relapses1-4; however, in some cases it is necessary to use immunsuppressants such as cyclophosphamide, azathioprine, methotrexate,1,4,13-19 and cyclosporin A.3,4,18,20 Other treatments that have been employed for cases that are refractory to previously mentioned medications include colchicine4,21 and dapsone22,23, biologic therapy with anti-CD4,4,18 and against tumor necrosis factor alpha have been recently used, obtaining good responses; nonetheless, infections, occasionally serious, have been the most frequent adverse event present, making it necessary to carefully ponder their administration to immunodeficient patients.4,24,25 Complete remission after autologous stem-cell transplant has been reported, and Navarro et al have described an adequate response with the use of daily, oral bovine type II collagen.4 Because of the respiratory compromise present in these patients, some require permanent tracheotomy, the installation of bronchial or tracheal stents and mechanic ventilation with continuous positive pressure.26-28 Its course can be lethal, in 50% of cases due to dyspnea that arises after collapse of the respiratory airways, recurrent pneumonia, and other renal and cardiovascular complications; as well as vasculitis, which can also lead to a very poor prognosis.1,2,4,17 In this study we analyze the epidemiologic, clinical, and therapeutic aspects in a series of patients from 3 rheumatology centers.

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loss in 4 (36.3%), and dysphonia in 4 (36.3%); the rest of the manifestations are present in Figure 4.

Complications reported during follow-up were: subglotic stenosis in 4 (36.3%) patients; eye lesions (18.8%), 2 patients (13.3%) had episcleritis and 1 (9%), retinal and corneal detachment with a macular lesion; hearing problems, 2 (18.8%) had conductive and sensory hearing loss; renal lesions, glomerulonephritis in 2 (18.8%), and cardiovascular lesions, 1 (9%) case of mitral and tricuspid insufficiency.

All patients with subglotic stenosis underwent permanent tracheotomy; 1 patient needed a corneal transplant due to corneal detachment.

RP was associated to other diseases in 5 patients: systemic lupus erythematosus (1) and Sicca syndrome (1) diagnosed at the same time as RP, psoriasis (1) 12 years before the diagnosis of RP, goiter (1) 4 years after diagnosis, and a history of diabetes mellitus (1), with no specific time since onset given.

All of the patients received prednisone-based treatments initially. Cases that did not respond to steroids received, in addition to steroids: cyclophosphamide, methotrexate, and azathioprine, among the most used. Doses and means of delivery are described in Table.

Other treatments employed were: colchicine, at a dose of 0.6 mg/kg in 1 (6.6%) patient and dapsone in another; however, this patient suspended treatment due to gastric intolerance.

Other drugs were also employed, according to the comorbidities, such as hydroxichloroquine and antiepileptic drugs in a patient with central nervous system lupus.

The use of intranasal steroids and ocular steroids was based on the affection present on these sites.

The main modifications to treatment were in the form of intravenous pulse steroids or pulse cyclophosphamide, or other immunosuppressants orally; the main reasons for these modifications were: a) glomerulonephritis; b) steroid-sparing; c) airway damage; d) relapse; and e) eye affection.

With regard to intravenous pulses, methylprednisolone was administered for 3 consecutive days for the treatment of acute manifestations, and in the case of cyclophosphamide, it was administered monthly for 6 months. In general, there were no adverse events due to medication, both at the beginning and during follow-up.
Discussion

RP is a rare disease, with approximately 600 cases worldwide.1,14 In Mexico, the first reported series was published by Lifshitz et al29 in 1986, with 7 cases, and afterward, in 2001, Meza et al1 presented 5 cases. With the patients in the present series, there are no more than 22 registered cases in the past 30 years, confirming a low frequency of this disease in our country, similar to what is reported worldwide.

Similar to what has been published, women predominated among our patients and the illness started on average around 40 years of age. With regard to the clinical manifestations, ear chondritis was the most frequent, affecting up to 72.7% of patients, which coincides with previous series where it is recorded in 35% to 89% of cases.1,34 Arthritis is the second most common manifestation communicated1,3,4,30,31; however, in our patients it was placed 5th, in 20% of cases. Hearing loss (36.3%), dysphonia (36.3%), and nasal chondritis (26.6%) were the second most frequent group of manifestations, coinciding with data from other series. Approximately 50% of patients have larynx and trachea involvement.3,14,28 During the follow-up in our series, subglotic stenosis was present in 4 patients that required permanent tracheotomy.

The association with other autoimmune diseases was present in 45.4% of cases, as has been communicated in previous studies.1,3,4,32 There was no predominance in the association with any other illness, and the moment in which it presented itself was also indistinct. Due to the scarcity of this disease, the diagnosis of RP can be delayed up to 1 or 2 years, and delays of up to 20 years have been described.5 In our patients, most cases were diagnosed in a period of 4 months to 4 years, which has implications such as the delay in the start of treatment, compromising the evolution of the disease and the prognosis of the illness and that is associated with irreversible complications such as hearing loss or respiratory manifestations.

Because the etiology is still unknown, there is no established therapeutic strategy. In this series all of the patients received initial treatment with steroids and these were used during their follow-up also, similar to the cases reported in other series, attaining an improvement in the initial symptoms. Unfortunately, progression of the disease persists in many cases, making it necessary to add other medications, such as immunosuppressants, orally or through intravenous pulse. There are no defined criteria to establish the moment in which an immunosuppressant should be added. In the case of our patients, the decision to employ immunosuppressant medications depended on the fact that the initial manifestations were considered “severe” by the attending physician, or that during the course of the disease there was evidence of a poor response to steroid treatment, defined by manifestations such as glomerulonephritis or episcleritis, that were not detected at the beginning of the disease; another parameter was relapse, but without setting a number of events as an indicator to make such a decision.

The reasons to use one immunosuppressant or another were not determined either; we observed a tendency to employ methotrexate and azathioprine, useful in refractory cases or as steroid-sparing drugs.18 No patients received cyclosporin A, which has been useful in refractory cases.20 Recently, the use of biologic therapy, such as anti-CD4 and infliximab (tumor necrosis factor alpha antagonist)10,24,25,33; no patients in this series received this type of treatment.

This series allows the observation that RP is still rare in Mexico, with similar epidemiologic characteristics to other populations, with treatment in general depending on the attending clinicians criteria, and observing an initial tendency to use steroids and immunosuppressants in patients that do not respond to steroids or have “several” relapses; of these medications, methotrexate and azathioprine were the most employed, with good overall results.

The diffusion of the knowledge about this disease is necessary, mainly among primary care physicians, where patients can simply be treated with non-steroidal anti-inflammatory drugs as monotherapy, or receive steroids; all of those measures can modify the course of disease and delay a definite diagnosis. Given the severity of the disease, the absence of consensus on treatment and the lack of knowledge on the “reversibility” of structural changes in type II collagen, based on our experience we propose a therapeutic strategy that includes the use of combined therapy once the diagnosis is established (steroids + methotrexate, steroids + azathioprine). Colchicine and dapsone can be used additionally to established therapy if improvement is not evident. The indication for cyclophosphamide must be considered an additional option in severe cases that do not respond to the previous triple-drug strategy.

Biologic therapy is less well documented than the previous treatments and its indication is left up to the clinician.

References


