Policondrite Recidivante, uma Apresentação sob a Forma de Esclerite Bilateral

Bilateral Scleritis as a Presenting Manifestation of Relapsing Polychondritis

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Resumo:

A policondrite recidivante é uma condição inflamatória rara com fisiopatologia ainda pouco conhecida e de origem incerta. É caracterizada por episódios recorrentes de inflamação envolvendo as cartilagens, predominantemente do pavilhão auricular, nariz e restantes articulações. Pode cursar com manifestações sistémicas, sendo potencialmente fatal quando cursa com envolvimento do trato respiratório. Atendendo à panóplia de manifestações clínicas, o diagnóstico é geralmente tardio. Neste momento, ainda não há consenso sobre os critérios de diagnóstico ou tratamento desta patologia.

Descreve-se o caso de uma doente com esclerite nodular anterior bilateral, como primeira manifestação de policondrite recidivante. A doença foi controlada inicialmente com corticosteróides, mas com recidiva, a motivar a introdução de metotrexato, com posterior estabilização clínica da doente.

Palavras-chave: Esclerite/diagnóstico; Metotrexato; Policondrite Recidivante/diagnóstico; Policondrite Recidivante/tratamento farmacológico.

Abstract:

Relapsing polychondritis is a rare inflammatory condition with poorly understood physiopathology and unclear origin. It is commonly characterized by recurrent episodes of inflammation involving cartilaginous tissues, predominantly those of the ears, nose and joints. It may also have systemic manifestations, which can have potentially severe complications, such following respiratory tract involvement. Diagnosis is typically delayed, due to this vast clinical spectrum and there is no consensus on the ideal diagnostic approach or treatment choice.

We report the case of a patient presenting bilateral anterior nodular scleritis as the first manifestation of relapsing polychondritis. We attained disease control with methotrexate therapy, following recurrent disease upon tapering of high dose corticosteroids.

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Keywords: *Methotrexate; Polychondritis, Relapsing/diagnosis; Polychondritis, Relapsing/drug therapy; Scleritis/diagnosis.*

Introduction

Relapsing polychondritis (RP) is characterized by relapsing inflammatory episodes, particularly chondritis, which leads to the progressive destruction of cartilage as it is progressively replaced with fibrous connective tissue with consequent deformity of these structures. Proteoglycan-rich tissues of the eye, heart, blood vessels, inner ears and skin may also be affected.[1-5]

The most common manifestations are auricular and nasal chondritis, however the clinical spectrum may vary from mild inflammatory episodes to life-threatening cardiopulmonary manifestations, such as airway collapse, heart failure due to valvular regurgitation or fatal rupture of aortic aneurysms. Up to half of patients have ocular symptoms, such as scleritis, episcleritis, uveitis, conjunctivitis, and keratitis.[4]

The etiology of RP remains uncertain, but its association with connective tissue diseases and systemic vasculitis suggests an immune-mediated condition. Moreover, autoimmune reactions to type II collagen have been demonstrated.[1-6] The real incidence and prevalence of this rare disease remain unknown.

Since there are no specific laboratory biomarkers or histologic findings the diagnosis of RP is established on a clinical basis (Table 1). The diagnostic approach and the optimal treatment choice continue to be non-standardized since there are still no randomized clinical trials available and most of our knowledge of the disease is based on case reports or case series.

Case Report

A 60-year-old female patient, with no relevant past medical history or chronic medication, reported episodes of alternating painful red eye, recurring once a month, over the past two years (Fig. 1). After ocular exam anterior nodular scleritis was documented.

A thorough investigation unveiled previous complaints of nasal pain during the red eye episodes, which improved under non-steroid anti-inflammatory drugs (NSAIDs). The patient also had one episode of swelling and redness in the right pinna

Table 1: Diagnostic criteria for relapsing polychondritis.

MCADAM *ET AL* CRITERIA[5] Three of the six following clinical features are necessary for diagnosis:
- Bilateral auricular chondritis - Nonerosive seronegative inflammatory polyarthritis - Nasal chondritis - Ocular inflammation - Respiratory tract chondritis - Audiovestibular damage
DAMIANI AND LEVINE CRITERIA[6] One of the following three sets is necessary for diagnosis:
- Three McAdam *et al* criteria - One McAdam *et al* criterion + positive histology results - Two McAdam *et al* criteria + therapeutic response to corticosteroid or dapsone therapy
MICHET *ET AL* CRITERIA[7] One of the following two conditions is necessary for diagnosis:
- Inflammation in two out of three: auricular, nasal, or laryngotracheal cartilages - Inflammation in one out of three above + two other signs including ocular inflammation, vestibular dysfunction, seronegative inflammatory arthritis, and hearing loss

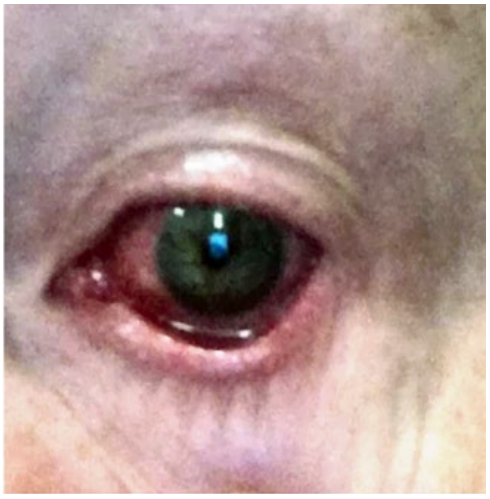

Figure 1: Left eye showing conjunctival hyperemia - during an episode of scleritis.

(Fig. 2). She denied joint pain or signs of arthritis. Following the association of auricular chondritis, possible nasal chondritis and ocular inflammation we considered a diagnosis of RP.

An initial workup revealed a slightly elevated C-reactive protein (CRP) (8.6 mg/L), with a normal erythrocyte sedimentation rate (ESR), no anemia and normal glomerular filtration rate. The diagnostic approach included an autoimmune workup that was unremarkable except for an anti-nuclear antibody titer of 1:160, with a mottled pattern. After a thorough investigation we excluded the possibility of an infectious cause.

The patient was then started on corticosteroids with a significant improvement of symptoms – on topical treatment for ocular inflammation and systemic treatment (oral prednisolone 1 mg/kg per day). Given the presence of scleritis, mild auricular chondritis and a therapeutic response to corticosteroids we assumed the clinical diagnosis of RP.[5-7]

Further investigation included a thoracic CT scan that did not show suggestive signs of airway involvement. Pulmonary function testing was unremarkable. A cartilage biopsy of the pinna was proposed but refused by the patient. A fibroscopy was performed, which did not document inflammatory signs or any lesion of the epiglottis or of the arytenoid cartilages. Moreover, no hearing impairment was documented. The patient also underwent a transthoracic echocardiography which excluded any valvular abnormalities.

Despite initial improvement, after two months of therapy, while attempting to taper bellow 20 mg/day, the disease relapsed, with multiple episodes of bilateral auricular chondritis and bilateral altering scleritis. Due to uncontrolled disease and documented resistance to corticotherapy, immunosuppressant treatment with methotrexate was started. After four months of follow-up, the disease has been controlled with increment doses of this drug (15 mg/ per week at the time of writing this article), allowing prednisolone to be progressively tapered.

To date, no other manifestations of the disease have manifested themselves, treatment has been very well tolerated with no reported adverse effects.

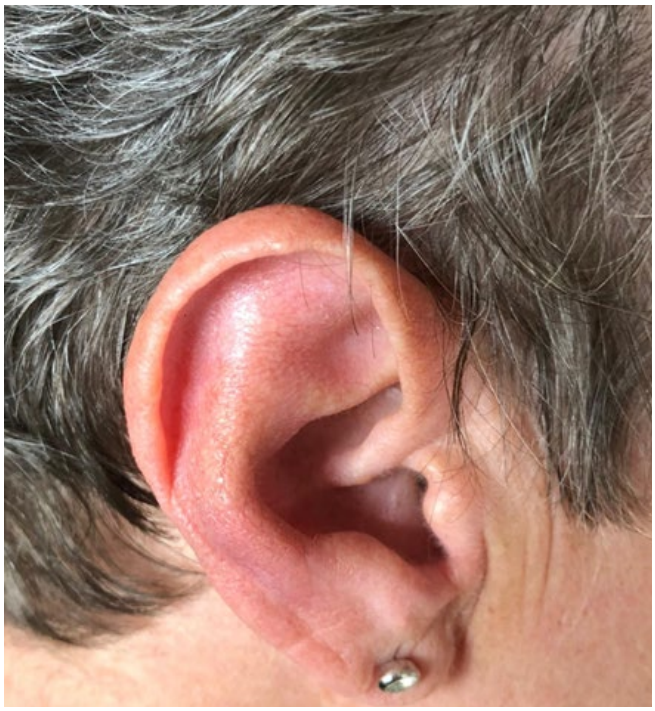

Figure 2: Auricular chondritis during acute phase- swelling and erythema of the cartilaginous part of the ear (pinna), sparing the lobule which lacks cartilage.

Discussion

Relapsing polychondritis is an uncommon inflammatory disease, with unclear etiology and pathophysiology. Furthermore, the potential trigger for clinical flares is not known since there is a lack of detailed epidemiological data. There is also insufficient data regarding not only the diagnostic approach but also therapeutic management. Since the diagnosis is clinical, it is of utmost importance to establish diagnostic criteria in daily practice.

In 1976, McAdam proposed the first diagnostic criteria based on the incidence of specific organ involvement observed in 23 patients enrolled in that cohort.[5] A few years later, Damiani and Levine[6] proposed an extended version of these criteria while studying their 10-patient cohort and Michet *et al* finally established the most inclusive criteria.[7] (Table 1) It is important to underline that those criteria reflect the population enrolled in each series and have not been validated in larger studies. Hence, they may not cover the diversity of clinical manifestations of RP.[8]

In the present case the diagnosis was assumed based on Damiani and Levine criteria, including bilateral auricular chondritis, ocular inflammation (two McAdam criteria) and a positive therapeutic response to corticosteroids.

In regard to laboratory diagnosis, there are not yet any validated or specific diagnostic biomarkers. Frequent laboratory findings are the elevation of nonspecific indicators of inflammation like CRP and ESR during flares and its normalization with remission. Studies have shown that the anticollagen type II antibodies and antimatrilin type I antibodies are neither sensitive nor specific enough to be of use. Furthermore, even histologic analysis such as cartilage biopsy fails to exhibit any abnormalities in many cases, with specific findings are only demonstrated in one third of patients.[2]

In two reports, Yoshinori Taniguchi *et al* reported the clinical utility of ultrasonography. They revealed that color Doppler ultrasonography can not only detect auricular inflammation, but also differentiate it from other types of chondritis, therefore clarifying the diagnosis of RP. Furthermore, ultrasonographic findings in auricular and nasal lesions may reflect the degree of disease activity (corresponding to biopsy findings) and thus determine in a non-invasive manner the response to treatment.[9,10] This readily accessible, non-invasive imaging technique may be the future of the diagnostic pathway of this rare disease thus permitting an earlier diagnosis.

Dion J *et al*,[11] in a recent retrospective large cohort, described three distinct phenotypes based on clinical manifestations, disease progression and prognosis. They suggest the division of patients according to three clusters: "hematologic", "respiratory" and "mild". This interpretation itself reflects the heterogeneity of the disease, including its pathophysiological mechanisms. It may be clinically relevant to use this classification not only for the treatment choice but also to for prognostic reasons. In our case, the patient would be considered in the "mild" cluster, to date no manifestations of other involvements.

Since RP can affect multiple organs, its clinical presentation can vary significantly leading to delayed diagnosis or even to misdiagnosis. This is particularly relevant when the first manifestation is not the typical cartilage involvement. Our case is an archetypal example of this delay: the patient presented ocular involvement as the first clinical manifestation, and two years passed until a diagnosis was established. In fact, ocular tissue involvement has been noted in large case reports, with a varying prevalence between 20% to 61%, and with different ocular manifestations being described. The most frequently reported manifestations are episcleritis/scleritis, conjunctivitis and uveitis.[4] In our diagnostic approach we attempted to exclude other systemic manifestations by focusing our study on the organs known to be affected by the disease.

Many auto-immune disorders have been associated (preceding or coexistent) with RP, in as many as 30% of the cases described, mostly with rheumatoid arthritis.[3,5] Our patient did not exhibit to date, one year follow up, any further manifestations, nor other immunologic biomarkers suggestive of a concomitant auto-immune disease.

Regarding the therapeutic options, there is currently no consensus, and the existing strategies are based on case reports and on individual experience, discussed on a case-to-case basis: this is due to the absence of randomized controlled trials to establish evidence-based guidelines. The use of NSAIDs may be sufficient alone in episodic cases of auricular chondritis. However, forms of persistent chondritis or more severe cases, such as the eye involvement documented in our case, require prolonged corticosteroid therapy.[1,4] Methotrexate, a conventional synthetic disease-modifying antirheumatic has been used successfully, as a corticosteroid-sparing drug. Some reports on the use of biologic drugs, mostly TNF-antagonists, have shown encouraging preliminary results.[12,13] In this case, due to relapsing disease upon corticosteroid tapering with recurrent scleritis episodes, methotrexate was used with a favorable response and stable disease remission on follow-up.

The Relapsing Polychondritis Disease Activity Index (RPDAI) was proposed in 2012 as a first consensus scoring system to evaluate disease activity and help determine treatment efficacy. RPDAI considers the 28-day period before assessment and comprises 27 items with different attributed weights, ranging from one to 24 and a maximum score of 265.[14] Our patient scores 27 (scleritis; auricular chondritis; nasal chondritis).

In 2018, based on an international expert consensus, the same group proposed a disease-specific damage measuring tool – the Relapsing Polychondritis Damage Index (RPDAM).[15]

The list is made up of 17 items.

The use of these measuring tools not only supports clinicians in their daily practice, but also allows standardization in data collection, essential to ensure the quality of clinical trials.

Therefore, they may contribute to further research and a better understanding of this pathology, ultimately leading to the best care of patients

Conclusion

The rarity of this disease has been associated with a lack of clinical awareness. In fact, the diagnosis of RP is still based on clinical features since there are no specific laboratory biomarkers. Inflammatory episodes are recurrent and unpredictable, and there may be multiple presentations due to the disease's clinical polymorphism, requiring detailed anamnesis and physical examination. Radiology has demonstrated an increasing relevance in estimating disease activity. When cartilage involvement is not the first manifestation, the diagnosis can be markedly delayed. Until randomized controlled studies are available, the treatment of RP will remain empirical and based on personal experience and small cohorts. ■

Declaração de Contribuição

AP, HG, FB, AF – Redação do manuscrito e aprovação da versão final

MT – Mentora do artigo, revisão do manuscrito e aprovação da versão final

Todos os autores aprovaram a versão final

Contributorship Statement

AP, HG, FB, AF – Writing of the manuscript and final approval

MT – Article mentor, manuscript review and final approval

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