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Przemysław Borowy[1, 2]*, Jakub Smyk[1]*, Patrycja Major[1]*, Natalia Mglej[1], Bogdan Batko[1, 2]

[1]Department of Rheumatology and Immunology, Andrzej Frycz-Modrzewski Kraków University, Kraków, Poland
[2]Department of Rheumatology and Immunology, J. Dietl Hospital, Kraków, Poland
*These authors contributed equally to the study.

Use of mycophenolate mofetil in refractory relapsing polychondritis

ABSTRACT

Relapsing polychondritis (RP) remains a difficult-to-treat disease of unknown aetiology and uncertain prognosis. Based on McAdam's criteria, rheumatoid arthritis (RA) was diagnosed in a 51-year-old female patient, and sequential therapy with dapsone — followed by naproxen and methylprednisolone — was initiated without achieving full remission. During the following years, the patient developed new locations of polychondritis (nose, epiphyses of long bones) and episcleritis. Methotrexate (MTX) was started, which was changed to mycophenolate mofetil (MM) due to adverse effects, resulting in sustained clinical improvement. There were no relapses during the subsequent 12 months of follow-up. The use of MM with good therapeutic effect in our patient is one of the few reported cases of such therapy in a patient with RP.

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Key words: relapsing polychondritis; mycophenolate mofetil; humoral response; cellular response; biologics

INTRODUCTION

Relapsing polychondritis (RP) is a rare disease of autoimmune origin. The clinical picture is marked by recurrent episodes of inflammation of cartilage tissue, as well as involvement of proteoglycan-rich tissues: inner ear, eye, heart valves, large vessels, kidneys and skin. Relapsing polychondritis (RP) leads to airway obstruction [1], valvular heart defects and aortic aneurysms. The exact mechanism of RP is not understood. An immune-inflammatory background is suspected, following the exposure of new autoantigens in these tissues. The presence of HLA-DR4 antigens is a risk factor for RP [2]. Treatment includes dapsone, glucocorticosteroids (GCSs), and MTX. Therapy of MM, although common in autoimmune diseases, is not used for RP. To date, only a few trials of such treatment have been published [3]. This paper shows the efficacy of MM in a female patient who did not achieve remission with available therapies.

CASE REPORT

A 51-year-old female patient presented in 2016 with recurrent inflammation of the auricle with localised pain, swelling, redness and fever (Fig. 1). For the first 2 years, she was repeatedly treated with antibiotics and intermittently with oral GCSs, yielding only short-term therapeutic effects. Diagnostic tests were performed for deficiencies in cellular and humoral immunity (Tab. 1). The results of biochemistry indicated elevated inflammatory markers dependent on disease activity, vitamin D deficiency and dyslipidemia. Bacterial cultures from the nose, pharynx, skin and a tuberculin reaction test were performed several times. Hepatitis B virus (HBV) infection and hepatitis C virus (HCV) infection, human immunodeficiency virus (HIV) infection, and Lyme disease were excluded. No signs of autoimmunization were found: the results of antinuclear antibodies (ANA) and anti-neutrophil cytoplasmic antibodies (ANCA) tests were negative. Addi-

Address for correspondence:
Przemysław Borowy, MD, PhD, ul. Wasilewskiego 12/2, 30–305 Kraków, Poland;
e-mail: pborowy@mp.pl

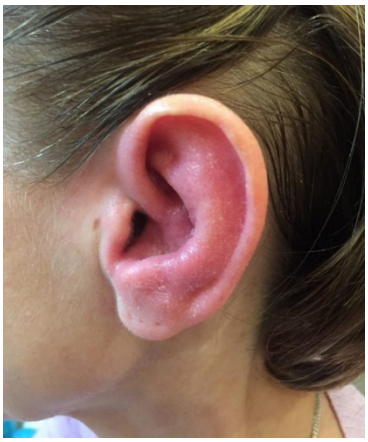

Figure 1. Right auricular chondritis

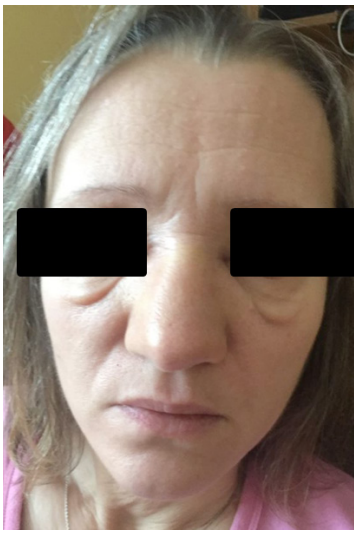

Figure 2. Swelling of the nasal bridge cartilage

tionally, the APS panel and anti-dsDNA by enzyme-linked immunosorbent assay (ELISA) showed no abnormalities. Rheumatoid factor (RF) and anti-CCP were normal. Lymphocyte response to mitogens and chemiluminescence test were normal. Imaging studies, radiographs (X-rays) of the extremities, lungs, ultrasound (US) scan of the joints did not reveal other potential causes of the disease. Based on clinical and laboratory data, good response to GCS treatment and the fulfilment of 4 out of 6 McAdam's criteria, RP was diagnosed and treatment with non-steroidal anti-inflammatory drugs (NSAIDs) was initiated. Since that time, the patient experienced six episodes of chondritis despite regular treatment with naproxen. For this reason, treatment with dapsone at a dose of 200 mg/d was attempted. After 2 months, its use was discontinued due to lack of improvement. Methylprednisolone was included. In April 2022, a further relapse occurred with a new site of inflammation: costochondritis, rhinitis (Fig. 2) and bilateral episcleritis. The patient was hospitalised and prednisolone at a dose of 40 mg and MTX were

Table 1. Lymphocytes and their subpopulations in peripheral blood (the study was performed by flow cytometry) and determinations of individual components of the complement system by radial immunodiffusion

Lymphocytes and their subpopulations				
	Percentage	**Norm**	**Number/μl**	**Norm**
Lymphocytes	27.0	21.9–48	1269	1130–3000
Lymphocyte subpopulations				
CD3	66	55–83	838	700–2100
CD4	36	28-57	457	300–1400
CD8	27	10-39	343	200–900
CD19	11	6–19	169	100–500
NK cells (CD3-16+ 56+)	15	7–31	230	90–600
Complement system components				
C3 [g/L]		1.06		
C4 [g/L]		0.24		
CH50 activity		Normal		
Immunoglobulin (Ig) levels				
IgA		1.7 (0.70–4.00 g/l)		
IgG		2.1 (0.40–2.30 g/l)		
IgM		2.7 (0.53–3.44 g/l)		
Ig subclasses G1–4		Normal		

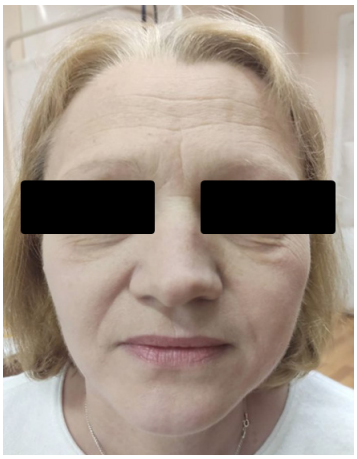

Figure 3. Apparent clinical improvement after treatment with mycophenolate mofetil and resolution of oedematous changes in the nasal cartilages.

started, with concomitant reduction of GCS doses. At 5 months, no complete remission was achieved and the patient needed continuous high doses of naproxen (1.0 g/d.). The patient did not tolerate MTX doses exceeding 15 mg/week. After one year of treatment, MTX was discontinued due to intolerance and treatment with MM at a dose of 2 g/d and prednisolone at a dose of 40 mg/d was started, gradually reducing it to a dose of 5 mg/d. Over the next 12 months of follow-up, there were no relapses, and the symptoms resolved. However, periodically, the patient required additional administration of naproxen (Fig. 3).

CRITERIA FOR THE DIAGNOSIS OF RP

The diagnosis of RP can be made based on several classifications. According to McAdam (Table 2), three out of six criteria are needed to make the diagnosis [4]. When assessing the patient's condition according to the Damiani and Levine criteria, a diagnosis is obtained when the patient shows a positive response to GCS treatment [5]. For the diagnosis of RP according to the Michet criteria, the fulfilment of two major criteria or one major and two minor criteria is sufficient [6].

DISCUSSION

Due to clinical course, the time between the onset of first symptoms and the diagnosis and implementation of appropriate treatment can take up to several years. The clinical criteria described above are useful. Joint involvement requires the exclusion of rheumatic, metabolic or infectious diseases. To date, there is a lack of publications that indicate an immune deficiency in RP. This paper is one of the few that analyse this problem, although the authors did not find any significant defects in humoral or cellular immunity. Other auto-

Table 2. Criteria for the diagnosis of relapsing polychondritis (RP) [4-6]

Criteria	Criteria for disease diagnosis:	Does it meet the criteria for disease?
Mc Adam	1) Relapsing bilateral auricular chondritis	**YES**
	2) Arthritis without the presence of erosions	**YES**
	3) Nasal chondritis	**YES**
	4) Ocular involvement (episcleritis)	**YES**
	5) Respiratory tract chondritis	NO
	6) Cochlear and/or vestibular dysfunction (resulting in unilateral or bilateral hearing loss)	NO
Damiani and Levini	1) Relapsing bilateral auricular chondritis	**YES**
	2) Arthritis without the presence of erosions	**YES**
	3) Nasal chondritis	**YES**
	4) Ocular involvement (episcleritis)	**YES**
	5) Positive response to GCS therapy	**YES**
Michet et al.	Major criteria:	
	1) Auricular chondritis	**YES**
	2) Nasal chondritis	**YES**
	3) Laryngeal and/or tracheal chondritis	NO
	Minor criteria:	
	1) Ocular inflammation	**YES**
	2) Seronegative arthritis	NO
	3) Hearing loss	NO
	4) Impairment of vestibular function	NO

immune comorbidities such as Hashimoto's disease, inflammatory bowel disease, vasculitis, type 1 diabetes mellitus, mixed connective tissue disease, systemic lupus erythematosus, and Behçet's disease have been described [7]. However, in this case, the patient did not have any coexisting diseases.

Treatment guidelines for RP are still lacking [8]. NSAIDs are used in mild forms of RP. Control of recurrent symptoms can also be achieved with dapsone (50–200 mg per day) or colchicine. Systemic GCSs are considered the treatment of choice. Oral prednisone is usually started at a dose of 0.25 to 1 mg/kg per day and gradually reduced. If disease symptoms are severe, intravenous pulses of methylprednisolone (500–1000 mg/day) may be used. Continuation of steroid therapy is often recommended for long-term follow-up to prevent relapses, but it does not affect the progression of the disease. For this reason, cyclophosphamide, azathioprine, cyclosporine and MTX are used alone or in combination with systemic GCSs for progressive disease [9]. Their use is also indicated in patients intolerant of GCSs or when they are ineffective [10]. The use of MM in RP was first and so far only described in a 50-year-old patient [3]. The use of MM with good therapeutic effect in the present case is another description of RP treatment. In one study in a group of 9 patients, tumour necrosis factor alpha (TNF-α) inhibitors were administered as first-line treatment. Partial or complete remission was achieved in seven cases [11]. The most commonly used drug was infiximab administered at a dose of 3–10 mg/kg every 6–8 weeks. Efficacy was maintained from 9 months to 3 years [12]. After considering the risk-benefit ratio, the authors of the publication concluded that TNF antagonists are effective drugs in the treatment of RP and can be administered as second-line GCS-sparing drugs [7]. Satisfactory response in RP refractory to standard treatment was achieved with tocilizumab [17]. However, evidence for the use of biologics comes from individual experience rather than randomised clinical trials. Therefore, their use is limited to patients who do not achieve a response to standard therapy.

CONCLUSIONS

Relapsing polychondritis (RP) remains a disease entity of unknown aetiology, with no identifiable disturbances in cellular and humoral immunity, exhibiting a variable course and proving difficult to treat. Currently, the clinician's experience, individual assessment of disease activity, and individual response to treatment are determining factors in the choice of therapy. In the presented case, the use of dual therapy with prednisolone and MM resulted in rapid clinical improvement. The use of MM is the second described case of successful treatment of RP. However, more evidence and longer follow-up are needed to recommend MM for the treatment of RP in the future.

AUTHORS' COMMENT

The diagnosis of RP is difficult if the clinical picture is limited to the auricle only and if relapses are rare. The two-year antibiotic therapy of the present patient is an example of this. In every case, a thorough differential diagnosis should be conducted by searching for potential triggering factors and comorbidities, taking into account scheduled therapy sessions. In this paper, the authors precisely assessed the patient's humoral and cellular immunity, finding no significant causative abnormalities. Long-term treatment aimed at controlling relapses and ensuring the safety of the patient poses an even greater challenge. Modifications to drugs are essential; therefore, a positive response to MM is a valuable addition to the "portfolio" of standard immunosuppressants and an indication to consider using MM in selected cases.

ETHICS STATEMENT

The authors declare that this paper as a case report does not disclose personal information about the patient. In the case of publishing accompanying photographs, patient anonymity has been preserved.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in relation to the submitted article.

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