D.G. Rekalov
I.O. Daniuk

Zaporizhzhia State Medical University, Zaporizhzhia, Ukraine

Key words: *relapsing polychondritis, infliximab.*

DOI: 10.32471/rheumatology.2707-6970.88.17102

A CLINICAL CASE OF SUCCESSFUL TREATMENT OF RELAPSING POLYCHONDRITIS WITH INFLIXIMAB

Introduction. *Relapsing polychondritis (RP) is a rare autoimmune disease characterized by recurrent episodes of the damages of cartilaginous and proteoglycan-rich structures of the ears, joints, nose, larynx, trachea, eyes, blood vessels, heart valves and kidneys.* ***Aim.*** *To demonstrate a case of achieving of stable remission using infliximab in patient with RP.* ***Case presentation.*** *A 30-year-old female with complaints of pain, burning and pulsation in the ears and eyes, pain and stiffness in the small joints of the hands during 2 months. In September 2018 was determined a diagnosis «Relapsing polychondritis, 1st attack, active phase, 2nd degree activity with damage to the external ears (chondritis), eyes (uveitis), small joints of the hands (non-erosive seronegative polyarthritis)». Using of steroids in medium doses led to side-drug effects. Remission for 6 months was reached by taking with dapsone 100 mg daily in combination with methylprednisolone 4 mg/daily, after which there was a second attack of the disease. After an ineffective repeated attempt to achieve remission with dapsone in combination with medium doses of steroids, a course of infliximab was started. After 4 infusions of infliximab was achieved a stable remission which lasted for 2 years. The third attack of the disease was characterized by minimal symptoms and remission was reached after 3 infusions of infliximab. Since April 2022 and until now, remission continues.* ***Conclusion.*** *Administration of infliximab for the treatment of RP can be considered as an alternative of GCs or cytostatic drugs in cases of mild or moderate severity without damage of vital organs.*

INTRODUCTION

Relapsing polychondritis (RP) is a rare autoimmune disease characterized by recurrent episodes of the damages of cartilaginous and proteoglycan-rich structures of the ears, joints, nose, larynx, trachea, eyes, blood vessels, heart valves and kidneys [1]. Genetic studies have identified HLA-DR4 as the major risk allele for RP, while a negative association exists between severity of organ involvement and HLA-DR6 [2]. The etiology of the disease remains unknown. During the period of high activity of the disease, high titers of antibodies to collagen types II, IX, XI, matrilin-1 have been detected in the serum of patients. Matrilin-1 is a protein of the intercellular matrix and is highly expressed in the tissues of the nose, trachea, ears, but not in the cartilaginous structures of the joints. Has been determined the negative correlation between disease activity and cartilaginous oligometric matrix protein, which is highly expressed in the intercellular space of cartilaginous elements of joints, ligaments and tendons which indicates the process of regeneration of cartilaginous structures during remission [3, 4, 5]. An increase of vascular endothelial growth factor, matrix metalloproteinase-3, monocyte chemoattractant protein-1, macrophage inflammatory protein 1-beta, interleukin-8, tumor necrosis factor-alpha (TNF-alpha) is observed in the blood, and immune complexes are detected in the affected cartilage structures. Deposits of T-lymphocytes (mainly CD4), macrophages, and plasma cells have been detected during biopsy in the affected cartilage structures. After several attacks ofthe disease, replacement of cartilaginous structures with connective tissue elements is observed [2, 6].

In typical cases RP has acute manifestation and characterized by damages of different organs, which contain cartilaginous tissue. In 85–90% of cases, the disease is manifested by acute inflammation of one or two ears. The main symptoms are pain, redness, throbbing, burning of the ear. Acute inflammatory episodes tend to resolve spontaneously within few days or weeks, with recurrence at variable intervals. In the absence of treatment, due to several attacks of the disease, the cartilage of the ear softens, replaces by fibrous connective tissue and deforms like «cauliflower ear». Hearing loss, which can be conductive or sensorineural, was demonstrated in as many as 46% of patients with RP, and vestibular dysfunction was documented in 6%. Inflammation of the vestibular structures or vasculitis of the internal auditory artery may cause sensorineural hearing loss [7, 8, 9].

Arthropathy appears approximately in 75–85% of patients. Joint involvements are characterized by asymmetrical and non-erosive seronegative damages of metacarpophalangeal, proximal interphalangeal joints, knees, ankle, wrists and elbows. Damage of the sterno-costal joints is typical [7, 10].

Ocular manifestations are observed in 50–60% of cases and included scleritis, episcleritis, conjunctivitis, uveitis, iritis, retinopathy and optic nerve damage [11].

Involvement of the respiratory tract in the pathological process occurs in 40–50% of cases and is manifested by cough, shortness of breath, hoarseness of voice, and pain in the trachea. Significant swelling of the larynx can be an indication for tracheotomy [12, 13]. Damage to the nasal cartilage is manifested by acute redness, pain, rhinorrhea, nasal congestion. Involvement of nasal bridge can lead to its destruction and «saddle nose» deformity in case of long course of disease [8].

Cutaneous manifestations (17–37% of cases) include papular rash, purpura, livedo, annular shape, located on the upper part of the body and distal ulceration and necrosis related to concomitant vasculitis. Histological examination has been detected the lymphocytic vasculitis without leukocytoclastic vasculitis [7, 14].

Renal dysfunction, which occurs approximately in 22% of patients, is characterized by increased of serum creatinine, proteinuria, and hematuria. Renal involvement is associated to poor prognosis, with a 10-year survival rate of 10%. Biopsy has been revealed moderate mesangial expansion and cell proliferation, segmental necrotizing glomerulonephritis, vascular and glomerular sclerosis. The immunofluorescence test has been detected the depositions of complement C3 and/or IgG or IgM (mainly in the mesangium) [8,15, 16].

Cardiovascular complications are diagnosed in 25% of patients with RP and include heart valve damage, myocarditis, pericarditis, aortic aneurysm, aortic dissection, atrioventricular block, and systemic vasculitis [7, 17, 18].

In 30% of cases RP is associated with other autoimmune diseases, such as systemic lupus erythematosus, scleroderma, mixed connective tissue disease, Sjögren's syndrome, dermatomyositis, spondyloarthropathies, rheumatoid arthritis, systemic vasculitis [19, 20]. An increase in the frequency of cases of RP is observed in people with myelodysplastic syndrome (MDS). It has been demonstrated that up to 27% of patients with MDS suffer from RP [21].

Laboratory changes in RP are nonspecific and include anemia, leukocytosis, thrombocytosis, increased erythrocyte sedimentation rate (ESR) and C-reactive protein. Detection of rheumatoid factor, ANCA, antinuclear, antiphospholipid antibodies indicates to an association with other rheumatic diseases and is not specific for RP [22, 23, 24].

According to McAdam et al. (1976), the diagnosis of RP can be made in case of presence of three or more clinical features: auricular chondritis, nasal chondritis, nonerosive inflammatory polyarthritis, ocular inflammation, respiratory tract chondritis, audiovestibular disoders [25]. In 1979 Damiani and Levine modified to McAdam's criteria, adding the presence of at least one McAdam criterion and positive histologic confirmation, or two McAdam criteria and positive response to administration of corticosteroids or dapsone [26].

In 2012, a global group of experts published the Relapsing Polychondritis Disease Activity Index (RPDAI) to standardize patient assessment and monitor response to treatment. It consists of 27 questions with an individual calculation of disease symptoms over a 28-day period (online calculator www.RPDAI.org) [27].

The goal of RP treatment includes achieving remission, preventing exacerbations and damages to vital organs. The most studied and effective group of drugs for the RP treatment is glucocorticoids (GCs). Medium, high and pulse-doses of prednisolone (especially with signs of damage to the cardiovascular system or kidneys) are used for achieving remission. Long-term using of low doses of GCs prevents escalation of the disease. Mild forms of RP can be controlled by taking dapsone (50–200 mg daily or colchicine 0.6 mg 2–4 times daily). For disease modification are used cyclophosphamide (1 mg/kg/day for two weeks, increasing the dose by 25 mg every two weeks), azathioprine (2 mg/kg/day), methotrexate 15–25 mg once a week, alone or in combination with GCS, especially in severe forms of RP with damage to vital organs [6, 28].

In recent years, studies have demonstrated some effectiveness of biological therapy in the treatment of RP. TNF inhibitors (infliximab 3–10 mg/kg every 6–8 weeks, etanercept 50 mg/week, adalimumab 40 mg/2 weeks) have showed the best results. The use of biologics is indicated in case of resistance or intolerance to GCs or to other immunosuppressive drugs. In addition, combination of GCs and biologic agents is not excluded [29, 30]. But the effectiveness and safety of the use of biologic agents in RP continues to be debated, so it is extremely important to record all cases of effective treatment of RP with biologics.

AIM

To demonstrate a case of achieving of stable remission using infliximab in patient with RP.

CASE PRESENTATION

A 30-year-old female fell ill suddenly in July 2018 with complains of pain, burning and pulsation in the right ear. Patient used NSAID with minimal effect. After 2 weeks, the symptoms appeared on the left ear, and pain, burning in the eyes began to bother. The patient was treated by an ophthalmologist for uveitis and received parabulbar injections of GCs — without a significant and long-term effect. At the same time, the patient began to be bothered by pain, swelling and morning stiffness in the small joints of the hands. An increase in ESR to 33 m/h, C-reactive protein to 22.8 mg/l, absence of rheumatoid factor and anti-CCP were detected. In September 2018 by rheumatologist was determined a diagnosis «Relapsing polychondritis,

1st attack, active phase, 2nd degree activity with damage to the external ears (chondritis), eyes (uveitis), small joints of the hands (non-erosive seronegative polyarthritis)». Using of methylprednisolone in dose of 16 mg/daily led to side-drug effects (insomnia, tachycardia, hypertension) without significant improvement. Remission for 6 months was reached by taking with dapsone 100 mg daily in combination with methylprednisolone 4 mg/daily (with slow cancellation of GCs). In June 2019 there was a second attack of the disease with similar complaints. After an ineffective repeated attempt to achieve remission with dapsone in combination with medium doses of steroids, a course of infliximab was started. After 4 infusions of infliximab was achieved a stable remission which lasted for 2 years. Also, patient took the methylprednisolone 4 mg/daily orally during 2 months after last infusion of infliximab. The third attack of the disease was appeared in December 2021 and characterized by minimal symptoms with complaints of pain and stiffness in joints of hands and knees. Remission was achieved after 3 infusions of infliximab without GCs. Since April 2022 and until now, remission continues.

DISCUSSION

RP is a rare autoimmune disease, the treatment of which presents clinical difficulties due to the variety of clinical manifestations. RP has a tendency to a continually progressive course, and the absence of standardized treatment guidelines. Long-term administration of low doses of steroids is able to control the progression of the disease in the majority of patients. In the case of damage to vital organs (heart, aorta, kidneys, severe damage to the organs of vision or the vestibular apparatus), a combination of cytostatics and GCs is most appropriate. But in some cases taking GCs or cytostatics is associated with side-drugs effects, treatment resistance or patient's refusal. Due to the latest data, alternative is using biologic agents. In the epoch of biological therapy, the study of all cases of RP in which the use of immunobiological drugs has demonstrated a clinical effect is extremely relevant.

Our article presents a clinical case of RP with moderate activity without damage to vital organs, so there were no indications for GCs pulse-therapy or cytostatic administration. Attempt to achieve clinical remission by taking methylprednisone caused to side-drug effects and patient's refusal to continue taking it. Using of dapsone did not provide long-term remission and did not show a clinical effect in case of a repeated attack. We decided to use infliximab, which had shown efficacy in the treatment of RP in some studies. After the introduction of 4 infusions of infliximab, we received a clinical remission that lasted almost 2 years. The third attack of the disease was characterized by articular manifestations without involvement of the vision and hearing organs, and it was possible to achieve remission after the introduction of 3 infusions of infliximab. Thus, we suppose that the use of infliximab is appropriate in cases of mild or moderate severity as GCs or cytostatics alternative.

CONCLUSION

Administration of infliximab for the treatment of RP can be considered as an alternative of GCs or cytostatic drugs in cases of mild or moderate severity without damage of vital organs.

REFERENCES

1. **Horvath A., Pall N., Molnar K. et al.** (2016) A nationwide study of the epidemiology of relapsing polychondritis. Clin. Epidemiol., 8: 211–30. doi: 10.2147/CLEP.S91439.

2. **Arnaud L., Mathian A., Haroche J. et al.** (2014) Pathogenesis of relapsing polychondritis: a 2013 update. Autoimmun. Rev., 13: 90–5. doi: 10.1016/j.autrev.2013.07.005.

3. **Foidart J.M., Abe S., Martin G.R. et al.** (1978) Antibodies to type II collagen in relapsing polychondritis. N. Engl. J. Med., 299: 1203–1207. doi: 10.1056/NEJM197811302992202.

4. **Alsalameh S., Mollenhauer J., Scheuplein F. et al.** (1993) Preferential cellular and humoral immune reactivities to native and denatured collagen types IX and XI in a patient with fatal relapsing polychondritis. J. Rheumatol., 20(8): 1419–1424.

5. **Saxne T., Heinegard D.** (1995) Serum concentrations of two cartilage matrix proteins reflecting different aspects of cartilage turnover in relapsing polychondritis. Arthritis Rheum., 38: 294–296. doi: 10.1002/art.1780380224.

6. **Vitale A., Sota J., Rigante D.** (2016) Relapsing Polychondritis: an Update on Pathogenesis, Clinical Features, Diagnostic Tools, and Therapeutic Perspectives. Curr. Rheumatol. Rep. Jan. 18(1): 3. doi: 10.1007/s11926-015-0549-5.

7. **Tlysh M.M., Kuznetsova T.H., Naatyzh Zh.Iu.** (2018) Retsydyvyruiushchyi polykhondryt v praktyke vracha-dermatovenerologa. Terapevtycheskyi arhiv, 1: 65–68. doi.org/10.26442/terarkh201890165-68.

8. **Borgia F., Giuffrida R., Guarneri F. et al.** (2018) Relapsing Polychondritis: An Updated Review. Biomedicines, 6: 84, doi: 10.3390/biomedicines6030084.

9. **Takwoingi Y.M.** (2009) Relapsing polychondritis associated with bilateral stapes footplate fixation: A case report J. Med. Case Rep., 3: 84–96. doi: 10.4076/1752-1947-3-8496.

10. **Balsa A., Expinosa A., Cuesta M. et al.** (1995) Joint symptoms in relapsing polychondritis. Clin. Exp. Rheumatol., 13: 425–430.

11. **Teo L., Choo C.T.** (2014) Orbital inflammatory disease in relapsing polychondritis. Orbit, 33: 298–301. doi: 10.3109/01676830.2014.902479.

12. **Carden K.A., Boiselle P.M., Waltz D.A. et al.** (2005) Tracheomalacia and tracheobronchomalacia in children and adults: an in-depth review. Chest; 127: 984–1005. doi: 10.1378/chest.127.3.984.

13. **Dubey S., Gelder C., Pink G. et al.** (2021) Respiratory subtype of relapsing polychondritis frequently presents as difficult asthma: a descriptive study of respiratory involvement in relapsing polychondritis with 13 patients from a single UK centre. ERJ Open Res., 7: 00170–2020. doi.org/10.1183/23120541.00170-2020.

14. **Tronquoy A.F., de Quatrebarbes J., Picard D. et al.** (2011) Papular and annular fixed urticarial eruption: A characteristic skin manifestation in patients with relapsing polychondritis. J. Am. Acad. Dermatol., 65: 1161–1166. doi: 10.1016/j.jaad.2010.09.007.

15. **Barzegar C., Vrtovsnik F., Devars J.F. et al.** (2002) Vasculitis with mesangial IgA deposits complicating relapsing polychondritis. Clin. Exp. Rheumatol., 20: 89–91.

16. **Lee J.E., Lee E.K.** (2012) A case of membranous nephropathy associated with relapsing polychondritis. Kidney Res. Clin. Pract., 31: 253–256. doi: 10.1016/j.krcp.2012.10.004.

17. **Le Besnerais M., Arnaud L., Boutemy J. et al.** (2018) Aortic involvement in relapsing polychondritis. Joint Bone Spine, 85: 345–51. doi: 10.1016/j.jbspin.2017.05.009.

18. **Sugrue G., Durcan L., Bell L. et al.** (2014) Unsuspected cardiovascular involvement in relapsing polychondritis: A case of aortitis with critical coronary artery stenosis secondary to relapsing

polychondritis. Circ. Cardiovasc. Imaging, 7: 409–411. doi: 10.1161/CIRCIMAGING.113.001290.

19. **Cantarini L., Vitale A., Brizi M.G. et al.** (2014) Diagnosis and classification of relapsing polychondritis. J. Autoimmun., 48: 53–59. doi: 10.1016/j.jaut.2014.01.026.

20. **Ludvigsson J.F, van Vollenhoven R.** (2016) Prevalence and comorbidity of relapsing polychondritis. Clin Epidemiol., 8: 361–2. doi: 10.2147/CLEP.S121272.

21. **Hebbar M., Brouillard M., Wattel E. et al.** (1995) Association of myelodysplastic syndrome and relapsing polychondritis: Further evidence. Leukemia, 9: 731–733.

22. **Piette J.C., El-Rassi R., Amoura Z.** (1999) Antinuclear antibodies in relapsing polychondritis. Ann. Rheum. Dis., 58: 656–657. doi: 10.1136/ard.58.10.656.

23. **Trinn C., Mátyus Z., Ujhelyi L. et al** (2014) Relapsing polychondritis with p-ANCA associated vasculitis: Which triggers the other? World J. Clin. Cases, 2: 912–917. doi: 10.12998/wjcc.v2.i12.912.

24. **Harisdangkul H., Johnson W.W.** (1994) Association between relapsing polychondritis and systemic lupus erythematosus. South Med J., Jul; 87(7): 753–7. doi: 10.1097/00007611-199407000-00017.

25. **McAdam L.P., O'Hanlan M.A., Bluestone R. et al.** (1976) Relapsing polychondritis: prospective study of 23 patients and a review of the literature. Medicine (Baltimore). 55(3): 193–215.

26. **Damiani J.M., Levine H.L.** (1979) Relapsing polychondritis-report of ten cases. Laringoscope, 89(6): 929–44.

27. **Arnaud L., Devilliers H., Peng, S.L. et al.** (2012) The Relapsing Polychondritis Disease Activity Index: Development of a disease activity score for relapsing polychondritis. Autoimmun. Rev., 12: 204–209. doi: 10.1016/j.autrev.2012.06.005.

28. **Rednic S., Damian L., Talarico R. et al.** (2018) Relapsing polychondritis: state of the art on clinical practice guidelines. RMD Open, 4: e000788. doi:10.1136/rmdopen-2018-000788.

29. **Moulis G., Pugnet G., Costedoat-Chalumeau N. et al.** (2018) Efficacy and safety of biologics in relapsing polychondritis: a French national ulticentre study. Ann. Rheum. Dis., 77: 72–78. doi: 10.1136/annrheumdis-2017-212705.

30. **Mathian A., Miyara M., Cohen-Aubart F. et al.** (2016) Relapsing polychondritis: a 2016 update on clinical features, diagnostic tools, treatment and biological drug use. Best Pract. Res. Clin. Rheumatol., 30: 316–33. doi: 10.1016/j.berh.2016.08.001.

КЛІНІЧНИЙ ВИПАДОК УСПІШНОГО ЛІКУВАННЯ ІНФЛІКСИМАБОМ РЕЦИДИВУЮЧОГО ПОЛІХОНДРИТУ

Д.Г. Рекалов, І.О. Данюк

Резюме. ***Вступ.*** *Рецидивуючий поліхондрит (РП) — рідкісне аутоімунне захворювання, що характеризується рецидивуючими епізодами ураження хрящових і багатих протеоглікана-ми структур вух, суглобів, носа, гортані, трахеї, очей, кровоносних судин, серцевих клапанів і нирок.* ***Мета.*** *Продемонструвати випадок досягнення стійкої ремісії за допомогою інфліксимабу у хворого на РП.* ***Клінічний випадок.*** *Жінка віком 30 років зі скаргами на біль, печіння і пульсацію у вухах та очах, біль і скутість дрібних суглобів кистей рук протягом 2 міс. У вересні 2018 р. встановлено діагноз «Рецидивуючий поліхондрит, 1-й напад, активна фаза, 2-й ступінь активності з ураженням зовнішніх органів вуха (хондрит), очей (увеїт), дрібних суглобів кистей (неерозивний серонегативний поліартрит)». Застосування глюкокортикоїдів у середніх дозах призвело до розвитку побічної дії. Ремісія протягом 6 міс досягнута на фоні прийому дапсону 100 мг/добу в поєднанні з метилпреднізолоном 4 мг/добу, після чого виник повторний напад захворювання. Після неефективної повторної спроби досягнення ремісії дапсоном у поєднанні з середніми дозами стероїдів розпочато курс інфліксимабу. Після чотирьох інфузій інфліксимабу була досягнута стійка ремісія, яка тривала 2 роки. Третій напад захворювання характеризувався мінімальною симптоматикою, ремісія була досягнута після трьох інфузій інфліксимабу. З квітня 2022 р. і дотепер триває ремісія.* ***Висновок.*** *Застосування інфліксимабу для лікування РП можна розглядати як альтернативу глюкокортикоїдам або цитостатичним препаратам у випадках легкого та середнього ступеня тяжкості без ураження життєво важливих органів.*

Ключові слова: рецидивуючий поліхондрит, інфліксимаб.

Адреса для листування:
69005, м. Запоріжжя, бульвар Центральний, 20