EFFICACY OF RITUXIMAB IN DIFFICULT TO TREATMENT PATIENTS WITH POLYMYOSITIS

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Abstract. *Inflammatory myopathies are a heterogeneous group of diseases rarely encountered in clinical practice. They primarily involve the transverse striated muscles, and in some cases there is also extramuscular involvement of the skin, lungs, joints, esophagus, heart. Acute forms of myositis, which are the most common, are associated with viral diseases and usually resolve spontaneously. Chronic forms usually have a subacute onset and unknown etiology. The presence of different clinical phenotypes and courses is associated with diversity in autoantibody production. Historically, the treatment of refractory forms of polymyositis and dermatomyositis has undergone significant dynamics. Data from various studies have been published that show a significant reduction in the symptoms of inflammation, but unfortunately some of these disease-modifying treatments could not be established in rheumatology practice as sufficiently effective. Limiting factors are the retrospective nature of these studies, as well as different inclusion and exclusion criteria. However, in recent years, more and more data have emerged that present rituximab as one of the promising molecules for the treatment of patients refractory to conventional synthetic disease-modifying antirheumatic agents We present a clinical case of a 40-year-old Caucasian man with onset of the disease – fever, asthenodynamia, muscle pain and weakness, pericardial and pleural effusions. The patient was treated with glucocorticoids, methotrexate, pulse therapies with methylprednisolone and cyclophosphamide, as well as pulse therapy with intravenous immunoglobulins. Due to the temporary effect of the treatment and the relapse of the disease, the patient was started on mycophenolate mofetil therapy (instead of methotrexate). However, a new peak in disease activity was reported, necessitating resumption of pulse therapies with methylprednisolone and cyclophosphamide. Due to the refractory course of the disease, the patient was treated with rituximab after signed informed consent. A significant reduction in disease activity and a good clinical and therapeutic effect were reported.*

Key words: *polymyositis, rituximab, clinical case*

Introduction

Inflammatory myopathies are a heterogeneous group of diseases rarely encountered in clinical practice. They primarily involve the transverse striated muscles, and in some cases there is also extramuscular involvement of the skin, lungs, joints, esophagus, heart [1]. Acute forms of myositis, which are the most common, are associated with viral diseases and usually resolve spontaneously [2]. Chronic forms are usually subacute in onset and of unknown etiology. About 10-15% of them are associated with an underlying malignancy, most often in patients with dermatomyositis [2]. The presence of different clinical phenotypes and courses is associated with diversity in autoantibody production [2]. This suggests the existence of different genetically determined mechanisms of individual clinical manifestations [1, 2]. Several subgroups of idiopathic myositis have been defined, classified as polymyositis (PM), dermatomyositis (DM), inclusion myositis (IBM), myositis in systemic diseases of connective tissue (SDCT), etc. [1].

Myositis was first described in 1863 by Wagner in a patient with significant skin rashes [1, 3, 4]. Later, publications appeared in the literature that inflammatory myopathies could also occur in the absence of skin involvement [1, 3, 4].

The disease is diagnosed on the basis of anamnesis, physical status, and complex investigations, including an elevated serum level of muscle enzymes and the presence of autoantibodies in the serum, muscle weakness testing, electromyography, and biopsy. In recent years, the place of imaging diagnostics – in particular magnetic resonance imaging (MRI) – has become more and more widespread in clinical practice. On electromyography and magnetic resonance imaging (MRI), both diseases (PM and DM) show overlapping features. Despite these similarities, they can be distinguished from each other by the histological features of a biopsy [5]. From

an immunological point of view, certain differences are also established. Dermatomyositis is a humorally mediated disease, whereas polymyositis has a T-cell mediated response [6]. In both diseases, characteristic antibodies are found, which are classified as myositis-associated autoantibodies (MAA) (which can be found in patients with other SDCT) and myositis-specific antibodies (MSA), which are mainly found in patients with myositis [1, 7].

The main means of treatment are glucocorticoids (GC) in combination with immunosuppressants (IS). Prognosis is variable, with the majority of patients developing chronic disease with relapses over time. One of the antibodies with the greatest specificity is anti-Jo1. According to literature data, 90% of Jo-1 positive patients have muscle disease [5]. Other authors provide conflicting results regarding the association of anti-Jo-1 and PM/DM. Anti-Jo-1 has been found to be more associated with PM than DM in several studies [8, 9]. In contrast to these results, another study showed that anti-Jo-1 was almost equally present in PM and DM patients [10]. These differences may be due to various demographic differences [11]. Furthermore, data from recent studies have shown that anti-Jo-1 titers are associated with disease activity [11-14].

Clinical case

We present a 40-year-old Caucasian male. At the beginning of 2016, the disease debuted with 2 months of fever, asthenodynamia, muscle pain and weakness, pericardial and pleural effusions. Then he was hospitalized in the Military Medical Academy (MMA) – Sofia. Infectious and neoplasmic genesis of the complaints, as well as disorders in the function of the thyroid gland, based on numerous laboratory, microbiological and imaging studies, were rejected. Based on the described subjective complaints, EMG data of myogenic damage, increased levels of acute phase indicators, high serum levels of muscle enzymes and positive results of ANA-blot and myositis immunoblot, a diagnosis of Polymyositis was made. GC therapy was started with an initial dose of 1.5 mg/kg and a gradual reduction to a daily dose of 16 mg prednisolone equivalent. Against this background, in November 2016 and May 2017, two relapses were registered, controlled with pulse therapy methylprednisolone 1.0 g (PTMP) and pulse therapy intravenous immunoglobulin (PTIV). From the middle of May 2017, disease-modifying therapy with methotrexate (MTX) was initiated in a weekly dose of 20 mg, with a gradual reduction of the dose of GC to 10 mg daily.

After achieving low disease activity, a new relapse was registered in December 2018, again with fever, myalgias, arthralgias, muscle weakness, stiffness in the neck-shoulder and pelvic girdle, cough, high laboratory and immunological activity and proteinuria up to 1, 5 g for 24 hours. Then the patient was hospitalized in the Rheumatology Department of UMHAT Burgas and after screening for infections and neoplasms, a decision was made to initiate pulse therapy. Against the background of a weekly intake of 20 mg. MTX is carried out monthly PTMP 1.0 g, pulse therapies cyclophosphamide (PTCYP) 1.0 g, PTIV (400 mg/kg) for 6 consecutive months. The treatment with MTX was reported as ineffective and from 08.01.2019 it was replaced with Azatioprin 100 mg/day. Its intake is discontinued after a week due to the appearance of an upper dyspeptic syndrome. The therapy with MTX, in a weekly dose of 25 mg, together with the pulse therapy, is re-initiated. This therapeutic combination did not control the disease activity and was reported as ineffective. This necessitates, in July 2019, MTX to be replaced with Mycophenolate Mofetil 2 g daily per os, against the background of monthly PTMP. Three months later, partial remission was achieved with control of proteinuria and PTMP was discontinued. In maintenance treatment with MMF and GC 10 mg daily, at the end of April 2020, a new relapse was registered with fever up to 38.2 ºC, myalgias, muscle weakness and stiffness, right palmar-volar swelling, arthralgias, high immunological and laboratory activity, leukocytosis. The serum level of creatine phosphokinase reaches a level > 7000 U/l. Taking into account the already accumulated experience with the patient, it is estimated that PTMP and PTCYP have a rapidly exhausting effect and do not lead to permanent suppression of disease activity.

After signing an informed consent, outside the summary of product characteristics and taking into account the data from the published clinical observations [2, 15, 16, 17]., on 28.04.2020 therapy with Rituximab at a dose of 700 mg was started. i.v. in four consecutive weeks. From May 2020 to November 2020, clinical and laboratory remission was achieved, with normalization of the serum CPK level with persistent autoantibody synthesis, but with normal values of the complement fractions. In order to maintain the achieved therapeutic result, the treating team decided to conduct maintenance disease-modifying treatment with Rituximab 500 mg i.v. every 6 months. On 01.11.2020, four days after the next infusion of Rituximab, the patient developed a tox-

oinfectious syndrome, with symptoms of GD, with a positive Covid-19 PCR (SARS CoV 2 RNA) test. A twenty-day treatment of the infection was carried out at home and hospital conditions, on 21.11.2020 he was discharged afebrile, without parenchymal changes on the control X-ray of the lungs, complete blood count and all biochemical parameters were normal, CPK – 95 U/l. Given the already published data on the risk of Rituximab administration in the conditions of Covid 19 [18, 19]., the next scheduled infusion for May 21 was postponed. By the end of September 2021, the patient is in clinical and laboratory remission. At the beginning of October 2021 a new relapse occurred, which was controlled with PTMP, immediately after which Rituximab was administered. The next Rituximab infusions will take place in April 2022 and October 2022. Two years after initiation of Rituximab treatment regardless of interruptions, the patient has been in clinical remission for about 1 year with normal laboratory parameters (Fig. 1).

Discussion

Genetic, cellular, humoral, immune factors, as well as environmental factors are participants in the etiopathogenesis of PM [2, 5]. The possible combinations of these factors over time also give us the diversity in the clinical manifestations of the disease. The decision for disease-modifying therapeutic behavior with Rituximab in the described case is based on the lack of effectiveness of conventional treatment with GC and IS, as well as on the data from the mentioned four publications on the application of this drug in a small number of patients with PM and DM. The reported results of our patient's treatment show a significant reduction in disease activity, which was assessed both by the normalization of acute-phase indicators and by a significant reduction and absence of clinical symptoms of inflammation of the joints, muscles, proteinuria and fever.

Oddis et al published the results of 200 patients diagnosed with treatment-refractory juvenile dermatomyositis and adult polymyositis for whom rituximab therapy was initiated. Of these, 161 (83%) met the definition of improvement. Data from the conducted study show that the treatment of inflammatory myopathies is a challenge for modern rheumatology, but a significant percentage of treated patients achieve the definition of improvement [17].

Most studies conducted so far have included separate reference centers. The data used for the analyzes performed were generally retrospective in nature for a small number of patients observed for relatively short periods of time. In addition, differences in inclusion and exclusion criteria complicate the assessment of treatment response, as disease impairment and the inclusion of misdiagnosed patients contribute to suboptimal therapeutic outcomes [17, 20]. Current recommendations for the treatment of PM/DM state corticosteroids as the primary therapy to be followed by various immunosuppressive or immunomodulatory agents alone or in combination, although glucocorticoids have not been formally tested in controlled trials [20]. Treatment with rituximab has shown promising results, which are consistent

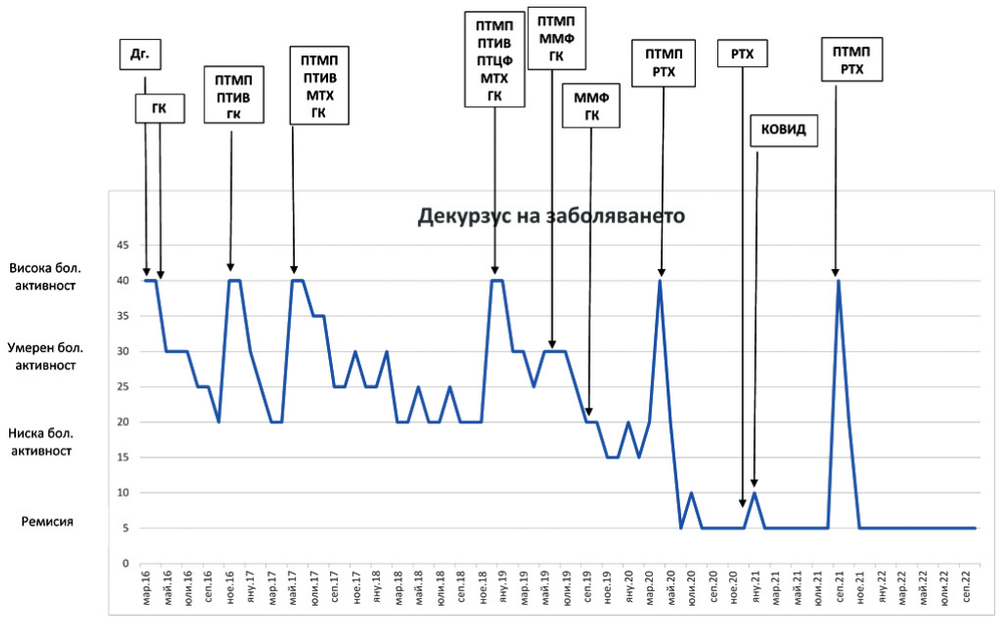


Fig. 1. Course of the patient's disease against the background of the ongoing therapy

with our clinical experience and the presented case. However, future research in this direction as well as prospective studies with unified criteria need to be conducted.

Conclusion

Conducting targeted scientific research at the genetic and immunological level in inflammatory myopathies in the future would help to define markers for reasoned selection of more precise targeted therapies.

Библиография / References

1. Raychaudhuri SP, Mitra A. Polymyositis and dermatomyositis: Disease spectrum and classification. Indian J Dermatol. 2012 Sep;57(5):366-70. doi: 10.4103/0019-5154.100477. PMID: 23112356; PMCID: PMC3482799.
2. Hochberg M, Silman A, Smolen J et al. Rheumatology, sixth edition 2015, p.1250 /tentative algorithm for management of inflammatory myopathies/ Levine TD, Rituximab in the treatment of dermatomyositis: an open- label pilot study.
3. Bohan A, Peter JB. Polymyositis and dermatomyositis (first of two parts) N Engl J Med. 1975;292:344–7.
4. Kovacs SO, Kovacs SC. Dermatomyositis. J Am Acad Dermatol. 1998;39:899–920.
5. Mammen AL. Dermatomyositis and polymyositis: Clinical presentation, autoantibodies, and pathogenesis. Ann N Y Acad Sci. 2010;1184:134–53.
6. Gherardi RK. Pathogenic aspects of dermatomyositis, polymyositis and overlap myositis. Presse Med. 2011;40:e209–18.
7. Hengstman GJ, van Brenk L, Vree Egberts WT, van der Kooi EL, Borm GF, Padberg GW, et al. High specificity of myositis specific autoantibodies for myositis compared with other neuromuscular disorders. J Neurol. 2005;252:534-7.
8. Fathi M, Vikgren J, Boijsen M, Tylen U, Jorfeldt L, Tornling G, et al. Interstitial lung disease in polymyositis and dermatomyositis: longitudinal evaluation by pulmonary function and radiology. Arthritis Rheum. 2008;59:677-85.
9. Klein RQ, Teal V, Taylor L, Troxel AB, Werth VP. Number, characteristics, and classification of patients with dermatomyositis seen by dermatology and rheumatology departments at a large tertiary medical center. J Am Acad Dermatol. 2007;57:937-43.
10. Selva-O'Callaghan A, Labrador-Horrillo M, Solans-Laque R, Simeon-Aznar CP, Martínez-Gómez X, Vilardell-Tarrés M. Myositis-specific and myositis-associated antibodies in a series of eighty-eight Mediterranean patients with idiopathic inflammatory myopathy. Arthritis Rheum. 2006;55:791–8.
11. Yoshida S, Akizuki M, Mimori T, Yamagata H, Inada S, Homma M. The precipitating antibody to an acidic nuclear protein antigen, the Jo-1, in connective tissue diseases. A marker for a subset of polymyositis with interstitial pulmonary fibrosis. Arthritis Rheum. 1983;26:604–11.
12. Miller FW, Twitty SA, Biswas T, Plotz PH. Origin and regulation of a disease-specific autoantibody response. Antigenic epitopes, spectrotype stability, and isotype restriction of anti-Jo-1 autoantibodies. J Clin Invest. 1990;85:468–75.
13. Stone KB, Oddis CV, Fertig N, Katsumata Y, Lucas M, Vogt M, et al. Anti-Jo-1 antibody levels correlate with disease activity in idiopathic inflammatory myopathy. Arthritis Rheum. 2007;56:3125–31.
14. Bernstein RM, Morgan SH, Chapman J, Bunn CC, Mathews MB, Turner-Warwick M, et al. Anti-Jo-1 antibody: a marker for myositis with interstitial lung disease. Br Med J (Clin Res Ed) 1984;289:151–2.
15. Arthritis Rheum 2005; 52:601-7. Mok CC, Ho LY, To CH. Rituximab for refractory polymyositis: an open-label prospective study
16. Mahler EA, Blom M., Voermans NC at al. Rituximab treatment in pacients with inflammatory myopathies. Rheumatology (Oxford) 2011; 50: 2206-13.
17. Oddis CV, Reed AM, Aggarwal R., Rituximab in the treatment of refractory adult and juvenile dermatomyositis and polymyositis; a randomized, placebo-phase trial. Arthritis Rheum.2013; 65; 314-24.
18. Andersen KM, Bates BA, Rashidi ES, et al. Long-term use of immunosuppressive medicines and in-hospital COVID-19 outcomes: a retrospective cohort study using data from the National COVID Cohort Collaborative. Lancet Rheumatol. 2021 doi: 10.1016/S2665-9913(21)00325-8. published online Nov 15.
19. Simpson-Yap S, De Brouwer E, Kalincik T, et al. Associations of disease-modifying therapies with COVID-19 severity in multiple sclerosis. Neurology. 2021;97:e1870–e1885.
20. Rider LG, Miller FW. Deciphering the clinical presentations, pathogenesis, and treatment of the idiopathic inflammatory myopathies. JAMA. 2011;305:183-90.

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