A CLINICAL CASE OF RHEUMATOID ARTHRITIS AND PULMONARY RHEUMATOID NODULES TREATED WITH TOCILIZUMAB

S. Emin, V. Boyadzhieva, N. Stoilov, R. Stoilov

Clinic of Rheumatology, University Hospital "Sveti Ivan Rilski" – Sofia

Abstract. *Rheumatoid arthritis is the most common disorder of the spectrum of inflammatory arthropaties worldwide. It is a chronic autoimmune disease with clinical manifestation of symmetrical erosive polyarthritis of small and large joints in the upper and lower extremities. In some forms of the disease, involvement of other organs and systems is observed. The case report we present is of a young polymorbid patient, for whom we accepted the diagnosis of seropositive rheumatoid arthritis. In the course of treatment with Methotrexate, a rare manifestation of the disease with lung involvement was found, where multiple rheumatoid nodules were seen using several imaging methods. A biopsy of a nodule was done and histologically verified. Although rheumatoid nodules are the most common extra-articular manifestation of the disease (25%), pulmonary localization is very rare, varying between 1-5% according to different sources. The patient's comorbidities significantly limit the possibilities of treatment and makes it a therapeutic problem. Biologic therapy with an anti-IL-6 monoclonal antibody was initiated. On follow-up radiography 5 months later, the rheumatoid nodules had regressed.*

Key words: *rheumatoid arthritis, rheumatoid nodules, autoimmune diseases, biologic therapy*

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by symmetrical polyarthritis of upper and/or lower limbs. It is the most common rheumatic disorder from the group of inflammatory arthropaties. By 2020 approximately 17.6 million people worldwide suffer from rheumatoid arthritis [1]. In 40% of cases, at the time of diagnosis or during the course of treatment, extra-articular manifestations are also observed, which can involve the skin, eyes, kidneys, gastrointestinal tract, the nervous, cardiovascular and respiratory systems [2]. Although rheumatoid nodules are the most common extra-articular manifestation of RA, their location in the lung is relatively rare with an incidence of < 0.4% on chest radiograph to over 30% on lung biopsy [3, 4, 5] . This manifestation is observed more often in seropositive for rheumatoid factor men, smokers, with subcutaneous rheumatoid nodules and on long-term treatment with Methotrexate [5, 6, 7]. Rheumatoid nodules are stiff, painless formations, most often located subcutaneously on extensor surfaces such as the proximal forearm, fingers, heels, etc., preferentially in places subjected to repetitive microtraumatism. They can also be located in tendons, bursae, around the periosteum and joints. Less often, they are also localized in the internal organs [8, 9, 10].

Some patients with RA have extremely high titers of rheumatoid factors, other autoantibodies, and a pronounced inflammatory process, which are the main reasons for the appearance of extra-musculoskeletal complications. Therapy with biological disease-modifying antirheumatic drugs (bDMARDs), which block the main cytokines proven to be involved in the inflammatory process – interleukin-6 (IL-6), interleukin-1 (IL-1), which are increasingly used in the treatment of these manifestations [11]. In the last twenty years, the treatment of rheumatoid arthritis has experienced dynamic development. Tocilizumab (TCZ) is the first humanized anti-IL-6 receptor subunit alpha (anti-IL-6R) monoclonal antibody approved for the treatment of RA refractory to methotrexate or TNFα - inhibitors. Interleukin 6 is a pro-inflammatory cytokine that plays a key role in the pathogenesis of the auto-inflammatory process in RA, and blocking it leads to an effective influence on the inflammatory process and a reduction of the disease activity. The drug can be used both in combination with conventional DMARDs and as monotherapy [12, 13]. The progressively increasing number of patients undergoing biological treatment with TNFα-inhibitors, as well as anti-IL-6 and target-synthetic disease-modifying antirheumatic drugs (tsBMARDs), significantly reduced the disability of these patients and improved their quality of life [12, 14, 15].

Case presentation

A 35-year-old Caucasian woman with complaints of inflammatory pain and swelling in the right radio-carpal joint, severe pain and limited movement in both shoulder joints, morning stiffness for about 2 hours was examined. The pain worsened at night. These symptoms lasted two months before the first visit to a rheumatologist. The patient reported episodes of skin rashes on the capillitium and the extensor surface of the elbows, which, due to spontaneous disappearance, were not biopsied. During the stay in the Rheumatology Clinic, a musculoskeletal ultrasonography (MSUS) was performed on wrist, shoulder and small hand joints. Intraarticular (i.a.) effusion, 2nd degree synovitis, no PD (Power Doppler) signal in the radio-carpal joint, tenosynovitis of the common extensor tendon, without inflammatory changes in the flexor tendons of the right hand were found. On the left hand no significant inflammatory changes were seen. No bone erosions were visualized along the contour of the carpal bones of both hands. The examination of metacarpophalangeal joints and proximal interphalangeal joints did not reveal any effusion, synovitis and PD signal; no crystalline deposits were visualized. MSUS imaging demonstrated bursitis in the subacromial subdeltoid bursa (SASD), exudative tenosynovitis of the long head of the biceps brachii muscle, and mild incipient degenerative changes in the left shoulder joint. X-ray of the hands and fingers showed juxta-articular reduced bone density, mildly narrowed joint spaces of the carpal joints with smoothly and sharply defined joint surfaces. Immunological studies showed highly elevated RF IgM, IgG, anti-CCP, anti-MCV (Table 1). Methotrexate 15 mg/week treatment was started and periarticular corticosteroid treatment was performed in the SASD bursa with immediate effect. The patient was diagnosed with two concomitant autoimmune diseases – Hashimoto's thyroiditis and type 1 diabetes mellitus. The patient has family history of psoriasis vulgaris (the patient's mother and sister).

Three months after the start of the therapy, the patient was found to have a complete lack of inflammatory activity. One year later, the patient developed adverse drug reactions (ADRs) to MTX (nausea and dizziness). During this period, she reported a feeling of chest pain, shortness of breath, and dry cough. X-ray of the lungs revealed annular ovoid shadows with a size of up to 23 mm in diameter visualized in the basal areas (Fig. 1). A similar shadow with a non-homogeneous appearance is found around the left hilus and the left subclavian area (Fig. 1).

Due to the limited informative value of the two-dimensional image, a high-resolution CT scan was performed. In the structure of both lungs, basally, as well as in the structure of the 6th segment on the left side, adjacent to the interlobar pleura, numerous scattered and different-sized nodules with uneven outlines were visualized. During video-assisted thoracoscopy (VATS), a biopsy of the finding was performed with subsequent histological examination of the material, confirming it as a rheumatoid nodule. Corticosteroid therapy with methylprednisolone 40 mg and Tocilizumab monotherapy intravenously was initiated. After 5 months of treatment with Tocilizumab, a follow-up radiography of the chest and lungs was performed, which confirmed regression of the rheumatoid nodules (Fig. 2). Corticosteroid treatment was reduced and discontinued within 6 months. Currently, the patient continues monotherapy with Tocilizumab and since 12 months she has been meeting both the Boolean of and Bulgarian Society of Rheumatology criteria for clinical remission [16, 17].

Table 1. Laboratory test results

Name of test	Result (reference range)
FBC, DBC, liver enzymes, creatinine, urea, Quantiferon	Within norm
ESR	35 mm/h (< 30)
CRP	13 mg/L (< 6)
RF IgM	> 500 U/ml (< 20)
RF IgG	318 U/ml (< 20)
Anti-CCP	118 U/ml (< 20)
Anti-MCV	170.3 U/ml (<20)
Tumor markers (NSE, Cyfra 21-1)	Within norm
ANCA	Negative
Anti-PR3	2.30 U/ml (< 5)
Anti-MPO	0.60 U/ml (< 5)
Bronchoalveolar lavage	No growth of yeasts and mold.
Histopathology of the biopsy	Histologic appearance of a rheumatoid nodule

X-ray Images

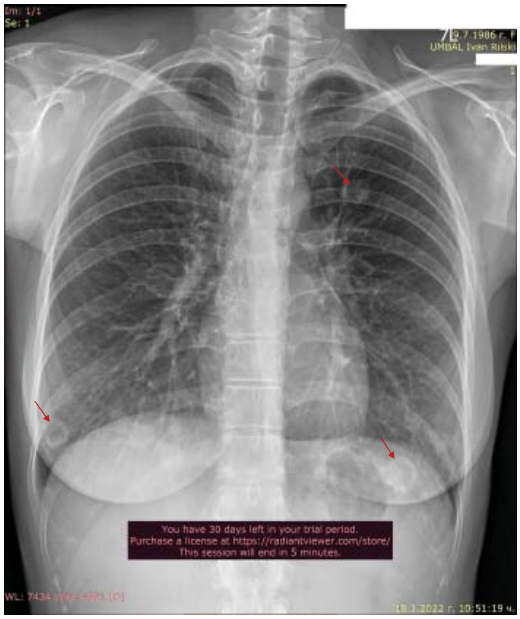


Fig. 1. X-ray of chest posterior-anterior view before treatment with tocilizumab



Fig. 2. X-ray of chest posterior-anterior view after treatment with tocilizumab

Discussion

With the diagnosis of rheumatoid arthritis, the patient collected a total of three separate autoimmune diseases (type 1 DM, Hashimoto's disease, RA). It has been found that 25% of patients with one autoimmune disease have a tendency to develop another.

Despite the diagnosis of RA at an early stage, the aggressive course of the disease manifested as pulmonary rheumatoid nodules.

Single or multiple small nodules may remain asymptomatic and be detected on routine chest radiography. Since pulmonary involvement is the second cause of mortality after cardiovascular complications in RA, when lung involvement is suspected, detailed imaging studies are needed, most often radiography, computed tomography (CT), chest scintigraphy. Due to the wide differential diagnosis, biopsy and histopathological examination of the findings is imperative.

The literature review shows clinical cases in which regression of pulmonary rheumatoid nodules was achieved under therapy with Tocilizumab and Rituximab [18, 19, 20, 21, 22]. In our patient, a therapy with Tocilizumab 8 mg/kg intravenously was initiated in July 2022. During a control X-ray of the chest in October 2022 rheumatoid nodules were not visualized anymore. As of May 2024 the patient continues monotherapy with Tocilizumab. When assessing the disease activity, clinical remission was established both according to DAS28-CRP (1.89), as well as according to the CDAI (2.5) and SDAI (3.3). Our case report confirms the published data to date. Treatment with Tocilizumab shows a significant effect both on the joint involvement in RA patients, as well as on the extra-articular manifestations of the disease [23,24,25,26,27].

Conclusion

The presented clinical case highlights the unpredictable course of rheumatoid arthritis, although it is detected at an early stage. The combination of three autoimmune diseases and this rare form of the disease with a wide differential diagnosis make the case a diagnostic and therapeutic challenge.

Библиография / References

1. GBD 2021 Rheumatoid Arthritis Collaborators. Global, regional, and national burden of rheumatoid arthritis, 1990-2020, and projections to 2050: a systematic analysis of the Global Burden of Disease Study 2021. Lancet Rheumatol. 2023 Sep 25;5(10):e594-e610. doi: 10.1016/S2665-9913(23)00211-4.
2. Cojocaru M, Cojocaru IM, Silosi I, Vrabie CD, Tanasescu R. Extra-articular Manifestations in Rheumatoid Arthritis. Maedica (Bucur). 2010 Dec;5(4):286-91.
3. Sagdeo P, Gattimallanahali Y, Kakade G, Canchi B. Rheumatoid lung nodule. BMJ Case Rep. 2015 Oct 29; 2015: bcr2015213083. doi: 10.1136/bcr-2015-213083.
4. Yousem SA, Colby TV, Carrington CB. Lung biopsy in rheumatoid arthritis. Am Rev Respir Dis. 1985 May;131(5):770-7. doi: 10.1164/arrd.1985.131.5.770.
5. Tilstra J S, Lienesch D W. Rheumatoid nodules. Dermatologic Clin. 33(3), 2015: 361-371.

6. Alhajery MA. Rheumatoid Arthritis With Multiple Lung Nodules: A Case Report. Cureus. 2024 Jan 16;16(1):e52350. doi: 10.7759/cureus.52350.
7. Chakraborty P P. Methotrexate-induced accelerated nodulosis in seropositive rheumatoid arthritis. JAPI, 2013 61(4): 274.
8. García-Patos V. Rheumatoid nodule. Semin Cutan Med Surg. 2007 Jun;26(2):100-7. doi: 10.1016/j.sder.2007.02.007.
9. Sayah A, English JC 3rd: Rheumatoid arthritis: A review of the cutaneous manifestations. J Am Acad Dermatol. 2005, 53:91-209,
10. Sibbitt WL Jr, Williams RC Jr: Cutaneous manifestations of rheumatoid arthritis. Int J Dermatol. 1982, 21:563-572.
11. Talotta R, Atzeni F, Batticciotto A. et al. Accelerated subcutaneous nodulosis in patients with rheumatoid arthritis treated with tocilizumab: a case series. J Med Case Rep. 2018, 2(1):154. doi: 10.1186/s13256-018-1687-y.
12. Biggioggero M, Crotti C, Becciolini A, Favalli EG. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. Drug Des Devel Ther. 2018 Dec 19;13:57-70. doi: 10.2147/DDDT.S150580.
13. McInnes IB, Buckley CD, Isaacs JD. Cytokines in rheumatoid arthritis – shaping the immunological landscape. Nat Rev Rheumatol. 2016;12(1):63-68.
14. De Stefano L, Guerini M, Pelizza J, et al. A case of a rheumatoid nodule on the aortic valve in a patient with rheumatoid arthritis in sustained remission with anti-TNFα. Scandinavian J Rheumatol, 2023, 52(5), 577–579. https://doi.org/10.1080/03009742.2023.2201065
15. Filippini M, Bazzani C, Atzeni F, et al. Effects of anti-TNF alpha drugs on disability in patients with rheumatoid arthritis: long-term real-life data from the Lorhen Registry. Biomed Res Int. 2014;2014:416892. doi: 10.1155/2014/416892.
16. Felson DT, Smolen JS, Wells G, et al. Rheumatism provisional definition of remission in rheumatoid arthritis for clinical trials. Arthritis Rheum. 2011 Mar;63(3):573-86. doi: 10.1002/art.30129.
17. Национален консенсус за лечение на ревматоиден артрит, Ревматология, 2020, 28, Приложение 2, 3-30. // National consensus for treatment of rheumatoid arthritis. Rheumatology. 2020, 28, Supp. 2, 3-30.
18. Andres M, Vela P, Romera C. Marked improvement of lung rheumatoid nodules after treatment with tocilizumab, Rheumatology, 2012, 51(6), 1132-1134, https://doi.org/10.1093/rheumatology/ker455
19. Braun M, Wagener, P. Regression von peripheren und pulmonalen Rheumaknoten unter Rituximab-Therapie. Z. Rheumatol. 2013, 72, 166-171. https://doi.org/10.1007/s00393-012-1054-0
20. Glace B, Gottenberg J, Mariette X, et al. Efficacy of rituximab in the treatment of pulmonary rheumatoid nodules: findings in 10 patients from the French AutoImmunity and Rituximab/Rheumatoid Arthritis registry (AIR/PR registry) Ann Rheum Dis. 2012;71:1429-1431.
21. Sargın G, Şentürk T. Multiple pulmonary nodules in rheumatoid arthritis. Eur J Rheumatol 2019; 6(4): 228.
22. Aksoy A, Kocakaya D, Yalçinkaya Y et al. Outcome of solid and cavitary pulmonary nodules in rheumatoid arthritis patients? case series, Turkish J Med Sci: 2022. 52: (5), 1713-1720. https://doi.org/10.55730/1300-0144.5514
23. Smolen JS, Beaulieu A, Rubbert-Roth A, et al. Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. Lancet. 2008;371(9617):987-997.
24. Genovese MC, McKay JD, Nasonov EL, et al. Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. Arthritis Rheum. 2008;58(10):2968-2980.
25. Emery P, Keystone E, Tony HP, et al. IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. Ann Rheum Dis. 2008;67(11):1516-1523.
26. Kremer JM, Blanco R, Brzosko M, et al. Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structu. Arthritis Rheum. 2011;63(3):609-621.
27. Biggioggero M, Crotti C, Becciolini A, Favalli EG. Tocilizumab in the treatment of rheumatoid arthritis: an evidence-based review and patient selection. Drug Des Devel Ther. 2019;13:57-70, https://doi.org/10.2147/DDDT.S150580.

Постъпил за печат: 17.07.2024 г.

Submitted: 17.07.2024

✉ *Адрес за кореспонденция:*
Д-р Сонер Емин
e-mail: dr.soneremin@gmail.com

✉ *Correspondence address:*
Soner Emin, MD
e-mail: dr.soneremin@gmail.com