RAPID DISEASE PROGRESSION IN A RHEUMATOID ARTHRITIS AND SYSTEMIC SCLEROSIS OVERLAP SYNDROME: A CASE REPORT

Valbona Duraj[1], Joana Hankollari[2], Ornela Gelaj[3], Jonida Xhixho[3], Ligea Gjoni[3]

[1]*Service of Rheumatology, University Hospital Center "Mother Teresa", Tirana, Albania*
[2]*Vorë Health Center, Vorë, Albania*
[3]*Resident in the Rheumatology Service*

Correspondent E-mail: valbonaduraj@yahoo.com

Abstract

Background: Rheumatoid arthritis is a chronic systemic inflammatory disease of an autoimmune nature. The small joints of the hands and feet are the primary targets, but it can also be associated with other joints or extra-articular involvement. Autoimmunity, vasculopathy, fibrosis are characteristics of systemic sclerosis, a chronic connective tissue disease. When patients meet diagnostic criteria for both diagnoses, they are considered to have the overlap syndrome. The treatment is individualized and focuses on the current clinical picture.

Case Report: A 57-year-old patient presents to her rheumatologist at her health center with pain in the small joints of the hands, objectively without signs of inflammation; RF, anti-CCP negative; ERS, CPR above normal justified by the viral condition. The patient did not meet the diagnostic criteria for any autoimmune rheumatic diseases. She had osteoarthritis of the hands. After 6-months, the follow-up visit resulted in the diagnosis of rheumatoid arthritis after the criteria were met. Due to mild pulmonary fibrosis, leflunomide 20 mg/day was initiated for treatment. Two months after starting therapy, the patient reported clinical improvement. Objectively, the small joints of the hands were without inflammation. About two months after the last check-up, Raynaud's phenomenon appeared and she left for Italy, where she was diagnosed with overlap syndrome of rheumatoid arthritis with systemic sclerosis, treated with leflunomide 20 mg/day, prednisone 5 mg/day, nifedipine 30 mg/day. When she returned, she was referred for hospitalization to the rheumatology service of University Hospital Center "Mother Teresa", where the same diagnosis was confirmed. She was treated with azathioprine 50 mg/day, prednisone 5 mg/day, and nifedipine 10 mg/day.

Conclusion: Patients with autoimmune rheumatic diseases require frequent monitoring because of the possibility of rapid progression of the disease, poor prognosis, and overlap syndromes.

Keywords: rheumatoid arthritis, systemic sclerosis, overlap syndrome

AVANCIMI I SHPEJTË I SËMUNDJES NË NJË SUBJEKT ME SINDROMËN E MBIVENDOSJES SË ARTRITIT REUMATOID ME SKLERODERIMINË SISTEMIKE: RAPORTIM RASTI

Abstrakt

Hyrje: Artriti reumatoid është një sëmundje inflamatore kronike sistemike me natyrë autoimune. Ai prek kryesisht artikulacionet e vogla të duarve, këmbëve, por mund të prekë dhe artikulacione të tjera apo prekje extra-artikulare. Sklerodermia sistemike është një sëmundje kronike e indit lidhor që karakterizohet nga autoimuniteti, vaskulopatia, fibroza. Sindromi i mbivendosjes së artritit reumatoid me skleroderminë sistemike ndodh në ato raste kur pacienti plotëson kriteret diagnostike për të dyja diagnozat. Trajtimi është i personalizuar dhe përqendrohet në kuadrin klinik mbizotërues.

Raportim rasti: Pacientja 57 vjeç, paraqitet te mjeku reumatolog në qendrën e saj shëndetësore me dhimbje të artikulacioneve të vogla të duarve, objektivisht pa shenja inflamacioni; FR, anti-CCP negativ; ERS, PCR mbinormë të justifikuara nga gjëndja virale. Pacientja nuk plotësonte kriteret diagnostike për asnjë sëmundje reumatizmale, largohet me diagnozën osteoartrozë e duarve. Në vizitën e rikontrollit, pas 6 muajsh, vendoset diagnoza artritit reumatoid pasi tashmë plotësoheshin kriteret dhe filloi mjekimin me leflunomide 20 mg/ditë për shkak të fibrozës së lehtë pulmonare. Dy muaj pas fillimit të terapisë, pacientja referoi përmirësim të klinikës, objektivisht artikulacionet e vogla te duarve pa inflamacion. Rreth dy muaj pas kontrollit të fundit i shfaqet fenomeni Raynaud dhe niset për në Itali, ku u diagnostikua me sindromën e mbivendosjes të artritit reumatoid me skleroderminë sistemike nën mjekim me leflunomide 20 mg/ditë, prednisone 5 mg/ditë, nifedipinë 30 mg/ditë. Kur rikthehet, referohet për hospitalizim në shërbimin e reumatologjisë QSUT, ku konfirmohet e njëjta diagnozë, nën mjekim me azathioprinë 50 mg/ditë, prednizon 5 mg/ditë, nifedipinë10 mg/ditë.

Konkluzione: Pacientët me sëmundje reumatizmale autoimune kanë nevojë për një monitorim të shpeshtë pasi ekzistojnë raste me një ecuri shumë të shpejtë të sëmundjes, prognozë jo të mirë dhe mund të shfaqen sindroma të mbivendosjes.

Fjalët kyçe: artrit reumatoid, sklerodermi sistemike, sindroma e mbivendosjes.

Introduction

Rheumatoid arthritis is a chronic systemic inflammatory disease of an autoimmune nature. The small joints of the hands and feet are the primary targets, but it can also be associated with other joints or extra-articular involvement (1). Based on 2010 Rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative, In order to diagnose rheumatoid arthritis, a minimum of 6 points of the diagnostic criteria must be met. The criteria are classified into clinical criteria, serological tests, acute phase inflammatory markers, and duration of symptoms. Clinical criteria include the number of affected joints. Serology assesses the positivity of FR and/or ACPA, including anti-CCP. ERS or CPR is measured to evaluate the level of disease activity,

and symptoms must have been present for at least 6 weeks. Joint involvement refers to any swollen or tender joint on examination, which may be confirmed by imaging evidence of synovitis. Distal interphalangeal joints, first carpometacarpal joints and first metatarsophalangeal joints are excluded from assessment. Categories of joint distribution are classified according to the location and number of involved joints, with placement into the highest category possible based on the pattern of joint involvement. Large joints refer to shoulders, elbows, hips, knees and ankles. Small joints refer to the metacarpophalangeal joints, proximal interphalangeal joints, second to fifth metatarsophalangeal joints, thumb interphalangeal joints and wrists. In this category, at least one of the involved joints must be a small joint; the other joints can include any combination of large and additional small joints, as well as other joints not specifically listed elsewhere (eg, temporomandibular, acromioclavicular, sternoclavicular, etc.) (2).

Systemic sclerosis is a heterogeneous disorder whose pathogenesis is characterized by 3 features: small-vessel vasculopathy, autoantibody production, and dysfunction of fibroblasts resulting in increased deposition of extracellular matrix. The American College of Rheumatology and European League Against Rheumatism (ACR-EULAR) created a joint proposal for new classification criteria in 2013. The ACR-EULAR classification criteria established that systemic sclerosis can be diagnosed if thickening of the skin of the fingers extends proximal to the metacarpophalangeal joints. Absent this finding, the presence of the following 7 features should be noted and scored: thickening of the skin of the fingers like puffy fingers or sclerodactyly, lesions on the fingertips like ulcers on tip of digits or pitting scars on fingertips, telangiectasia, abnormal nail fold capillaries, interstitial lung disease or pulmonary arterial hypertension, Raynaud phenomenon, and systemic sclerosis-related autoantibodies like presence of ≥1 of the following: Centromere antibody, Scl-70 antibody, RNA polymerase III antibody. Patients with a minimum score of 9 are classified with definite systemic sclerosis (3).

The presence of another rheumatological condition in patients with rheumatoid arthritis is not uncommon (4). Overlap Syndromes have been defined as entities satisfying classification criteria of at least two connective tissue diseases occurring at the same or at different times in the same patient. Connective tissue diseases include systemic lupus erythematosus , rheumatoid arthritis, systemic sclerosis, polymyositis/dermatomyositis, and Sjögren syndrome. Every combination of these disorders has been reported. In a recent study, 6.4% of systemic sclerosis patients studied was identified as having an overlap syndrome. The most frequent systemic sclerosis overlap syndromes reported were myositis in 42.8% and rheumatoid arthritis in 32%. It is known that there is a higher incidence of rheumatoid arthritis in systemic sclerosis patients than in the general population. Therefore, an active search for overlap syndromes should be performed in all patients (5, 6, 7, 8).

Case presentation

A 57-year-old patient presents to our health center with pain of an inflammatory and mechanical nature in the small joints of the hands and radiocarpal joints, which started a month ago. She reports that in the past she has suffered a fracture in the right glenohumeral joint and accidentally damaged the fifth digit of her right hand with a machine. According to her report, she is being treated for arterial hypertension and anxiety. There is no familial history of rheumatoid arthritis. She has performed basic laboratory control tests, which resulted within the norm. There is no record of any previous surgical interventions or drug or

non-drug allergies by her. The patient is experiencing a viral condition. During objective examination, the skin and mucous membranes were well-colored, the heart had rhythmic tones, bilateral vesicular respiration, a soft, palpable abdomen, bilateral negative Giordano test, the inferior extremities were slightly edematous bilaterally, and the vital parameters were normal. Small joints of the hands are not tender to pressure, and there are no signs of inflammation or infiltrations. Crepitation is present in knees during flexion and extension. The articular range of motion of other joints is preserved, but the right glenohumeral articulation is still tender. Normal cervical range of motion. No presence of rheumatoid nodules. Preserved muscular strength. No presence of Raynaud phenomenon, no skin induration. Oral aphthae, dry eyes or mouth, photosensitivity, or psoriatic cutaneous elements in the past or family history were not mentioned. It was recommended to complete the laboratory tests such as RF, anti-CCP, CRP, ERS, uric acid, posterior-anterior and oblique bilateral hand radiography. The hand radiograph showed only changes in favor of osteoarthritis of the hands. RF and anti-CCP were negative, uric acid 5.4 mg/dl, ERS 27 mm/h, CRP 13.6 mg/l. The latter was justified because of the viral condition that the patient was experiencing. She was diagnosed with hand osteoarthritis and treated with piroxicam 20 mg/day for only 10 days and oral hyaluronic acid (9). After two months of persistent pain, she visited a rheumatologist at a private institution. All laboratory tests were repeated, and the diagnosis of osteoarthritis of the hands was reconfirmed.

After 6 months from the first visit to our health center, the patient presented with the same pain, but this time with morning stiffness lasting over an hour, fatigue, body weakness, and knee pain. Our objective examination resulted in the discovery of tenderness, infiltration, and inflammation in the small joints of the hands, such as the proximal interphalangeal, metacarpophalangeal, and radiocarpal. Crepitus was present in her knees. Cervical and lumbar spine were slightly painful during maneuvers. The patient had meanwhile consulted a cardiologist for edema in the inferior extremities, and was recommended to repeat the basic control laboratory tests, ERS, CRP, RF, anti-CCP, uric acid, abdominal ultrasound, venous Doppler ultrasound of the inferior extremities and consult a pulmonologist in case of starting methotrexate therapy. Basic control laboratory tests within the norm, ERS 55 mm/h, CRP 27.71 mg/l, uric acid 2.88 mg/dl, RF slightly positive for the norm of the laboratory where it was performed 18.8 IU/ml, anti-CCP > 1000 U/ml. During a consultation with the cardiologist a few months ago, the patient was diagnosed with stage II arterial hypertension, hypertensive cardiopathy, dyslipidemia, without significant problems of the neck vessels, and was treated with enalapril and bisoprolol. Abdominal ultrasound showed grade II hepatosteatosis and cystitis. The venous Doppler ultrasound of both inferior extremities resulted without thrombosis. The presence of edema in the subcutaneous connective tissue of the bilateral distal thigh was found, with minimal tenosynovial changes in the posterior tibial and bilateral peroneal parts. During the consultation with the pulmonologist, the patient underwent pulmonary x-ray and spirometry. Moderate restriction was found, but it is noted that the patient performed the respiratory test with difficulty. It has been concluded that she has mild pulmonary fibrosis. The diagnosis of seropositive rheumatoid arthritis was made and due to pulmonary fibrosis, the patient started treatment with leflunomide 20 mg/day, she refused prednisone therapy (10). She was recommended to have a follow-up check after 2 months to monitor leflunomide therapy. After two months of treatment, the intensity of the pain has decreased, as well as the edema observed in the objective examination. A very mild normocytic anemia of 11.8 mg/dL and an increase in platelets of 512,000, with a high ERS of

45 mm/h were found. The family doctor was recommended to evaluate thrombocytosis and monitor hemoglobin levels.

After 8 months, she presented for a follow-up and reported that two months after the visit to our health center, she had Raynaud phenomenon when exposed to cold, and wounds for which she had started treatment in Italy, where she was diagnosed with rheumatoid arthritis-systemic sclerosis overlap syndrome and had started treatment with prednisone 5 mg/day, leflunomide 20 mg/day, nifedipine 30 mg/day, colecalciferol, aspirin 100 mg/day, lansoprazole, losartan, fluoxetine. On objective examination, the patient had Raynaud phenomenon, digital wound scars, deformed small hand joints, sclerodactyly, facial telangiectasia, and limited rima oris. In Italy, gastroparesis, mild pulmonary hypertension, and pulmonary fibrosis were also diagnosed. She was sent to the rheumatology service at the University Hospital Center 'Mother Teresa' for a health assessment and treatment. During hospitalization were found the following laboratory test results: anti-CCP 138.1 U/I, CPR 10.46 mg/l, positive ENA screen with positive anti-Scl 70 in ENA profile and normocytic anemia, ANA 1:480. Upon discharge, the diagnosis of overlap syndrome rheumatoid arthritis stage IV with systemic sclerosis (with gastroparesis and pulmonary fibrosis) was confirmed and treatment with azathioprine 50 mg/day, prednisone 7.5 mg/day, nifedipine 10 mg/day was initiated (11, 12, 13). After two weeks, the patient was hospitalized in the Internal Medicine Service at the University Hospital Center “Mother Teresa” due to dyspnea and arrhythmia, and she was discharged with the following diagnoses: anticoagulated paroxysmal atrial fibrillation, NYHA II heart failure, stage II arterial hypertension, systemic sclerosis, depression. After the second discharge, the patient was recommended to continue treatment with azathioprine and prednisone. Her normocytic anemia was probably caused by chronic disease and systemic sclerosis affecting the gastrointestinal tract. She reported that she had no epigastric pain, bleeding, melena, nausea, or vomiting, but only slight dysphagia when eating solid foods. This was the last time the patient came for a health check-up at our health center.

Discussion

According to a study conducted in Centre for Rheumatology, Royal Free Hospital, University College Medical School, London, between September 1999 and February 2007 that included in total, 332 (20%) of 1700 patients with systemic sclerosis (SSc) had overlap syndrome. This comprised myositis (42.8%), rheumatoid arthritis (RA; 32%), Sjögren's syndrome (SS; 16.8%), and systemic lupus erythematosus (SLE; 8.4%). Antinuclear antibody was positive in 96.6% of patients. Anticentromere antibody (ACA) was exclusively present in limited cutaneous systemic sclerosis overlap cases (22%), and more common in systemic sclerosis/Sjögren's syndrome overlap (44.7%), whereas no difference was found in the prevalence of Scl-70 autoantibody between limited cutaneous systemic sclerosis and diffuse cutaneous systemic sclerosis overlap groups. U1RNP was more frequent in SSc/SLE (44%), while Ro antibody was more likely to be found in SSc/SS overlap syndrome (29.8%). ACA was absent and anti-Scl-70 was infrequent in SSc/myositis; polymyositis-scleroderma antibody was more frequent in this group (33.1%). About 50% of patients had raised rheumatoid factor (RF), with no difference between overlap groups irrespective of RF titer. In contrast, anticyclic citrullinated peptide antibody was more frequent in patients with RA features. (7)

As presented in our case, the patient initially met the diagnostic criteria for hand osteoarthritis, within 6 months the typical clinical features of rheumatoid arthritis began and

the diagnostic criteria for seropositive rheumatoid arthritis were met. The overlap syndrome of rheumatoid arthritis with systemic sclerosis was confirmed while the patient manifested typical clinical features of systemic sclerosis. This happened after 5 months of the diagnosis of rheumatoid arthritis. The treatment was carried out in accordance with the patient's manifestations step by step. At the stage of hand osteoarthritis, nonsteroidal anti-inflammatory drugs were used, followed by leflunomide when rheumatoid arthritis was diagnosed due to mild pulmonary fibrosis and with azathioprine, prednisone, and nifedipine after hospitalization in the rheumatology service at the University Hospital Center "Mother Teresa". Such difficult cases with a very rapid course of the disease remind us that patients with autoimmune rheumatic diseases need frequent monitoring as there are cases with a very rapid course of the disease, poor prognosis and overlap syndromes may appear. (14)

Conclusion

Patients with autoimmune rheumatic diseases require frequent monitoring as there are cases with a very rapid course of the disease, poor prognosis, and overlap syndrome may occur. The overlap syndrome of rheumatoid arthritis and systemic sclerosis may require frequent hospitalizations for evaluation of gastrointestinal involvement, evaluation for possible pulmonary hypertension, evaluation of digital wounds, inflammation, and joint deformities, high disease activity and risk of serious cardiac and renal complications that can lead to sudden death.

Conflict of interest: The authors have no conflicts of interest to declare

References

1. Firestein and Kelley's Textbook of Rheumatology, 2:11th edition, Elsevier 2020, p.1181-1283.
2. Aletaha D, Neogi T, Silman AJ, et al. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative [published correction appears in Ann Rheum Dis. 2010 Oct;69(10):1892]. Ann Rheum Dis. 2010;69(9):1580-1588. doi:10.1136/ard.2010.138461
3. van den Hoogen F, Khanna D, Fransen J, et al. 2013 classification criteria for systemic sclerosis: an American college of rheumatology/European league against rheumatism collaborative initiative. Ann Rheum Dis. 2013;72(11):1747-1755. doi:10.1136/annrheumdis-2013-204424.
4. Luca Iaccarino, Mariele Gatto, Silvano Bettio, Francesco Caso, Mariaelisa Rampudda, Margherita Zen, et.al. Overlap connective tissue disease syndromes, Autoimmunity Reviews, 2013, Volume 12, Issue 3.
5. Pinto AS, Santos FC, Dinis SP, Madeira N, Ferreira JF, Vaz C. Systemic sclerosis and rheumatoid arthritis overlap syndrome - management of severe cardiac, pulmonary and articular involvement. Reumatologia. 2023;61(1):55-62. doi:10.5114/reum/161299.
6. Scherlinger M, Lutz J, Galli G, et al. Systemic sclerosis overlap and non-overlap syndromes share clinical characteristics but differ in prognosis and treatments. Semin Arthritis Rheum. 2021;51(1):36-42. doi:10.1016/j.semarthrit.2020.10.009

7. Pakozdi A, Nihtyanova S, Moinzadeh P, et al. Clinical and serological hallmarks of systemic sclerosis overlap syndromes. J Rheumatol 2011; 38: 2406–2409.
8. Jinnin M, Ihn H, Yamane K, et al. Clinical features of patients with systemic sclerosis accompanied by rheumatoid arthritis. Clin Exp Rheumatol 2003; 21: 91–94.
9. Haugen IK, Felson DT, Abhishek A, *et al* 2023 EULAR classification criteria for hand osteoarthritis *Annals of the Rheumatic Diseases* 2024;83:1428-1435.
10. Smolen JS, Landewé RBM, Bergstra SA, *et al* EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update *Annals of the Rheumatic Diseases* 2023;82:3-18.
11. Del Galdo F, Lescoat A, Conaghan PG, et al. EULAR recommendations for the treatment of systemic sclerosis: 2023 update. Ann Rheum Dis. Published online October 17, 2024. doi:10.1136/ard-2024-22643
12. Kowal-Bielecka, Otylia et al. "Update of EULAR recommendations for the treatment of systemic sclerosis." *Annals of the rheumatic diseases* vol. 76,8 (2017): 1327-1339. doi:10.1136/annrheumdis-2016-209909
13. Nassar M, Ghernautan V, Nso N, et al. Gastrointestinal involvement in systemic sclerosis: An updated review. *Medicine (Baltimore)*. 2022;101(45): e 31780.
14. Fujiwara, T., Tokuda, K., Momii, K. *et al.* Prognostic factors for the short-term mortality of patients with rheumatoid arthritis admitted to intensive care units. *BMC Rheumatol*. 2020; 4, 64.