Revista Română de Reumatologie
Romanian Journal of Rheumatology

CASE REPORT

Nothing Is Impossible: A Case Report of an Unusual Association of Rheumatologic Diseases

OANA-MĂDĂLINA MISTREANU[1,2], BIANCA-MARGARETA DUMITRESCU[1,2], CORINA-DELIA MOGOȘAN [1,2], CĂTĂLIN CODREANU[1,2]

[1] *"Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania*
[2] *"Dr. Ion Stoia" Clinical Centre for Rheumatic Diseases, Bucharest, Romania*

Abstract

Background: The coexistence of multiple rheumatic diseases in a single patient is uncommon but clinically significant.
Case Report: We report a 65-year-old female patient with rheumatoid arthritis (RA) and ankylosing spondylitis (AS), who developed subacute cutaneous lupus induced by sulfasalazine (DISL). AS was active so she was treated with secukinumab 150 mg monthly for five years, escalated to 300 mg due to cervical enthesitis. Partial response after five months led to a switch to etanercept, which improved joint symptoms but triggered DISL recurrence with anti-Ro52 positivity. Subsequently, sicca symptoms appeared, and Sjögren's syndrome was confirmed by biopsy. Upadacitinib 15 mg/day was initiated, resulting in remission of both musculoskeletal and cutaneous symptoms.
Conclusion: This case illustrates the diagnostic and therapeutic complexity of overlapping RA, AS, DISL, and Sjögren's syndrome. It underscores the risk of cutaneous adverse reactions to both synthetic and biologic DMARDs and highlights the importance of multidisciplinary monitoring and tailored treatment strategies.
Keywords: rheumatoid arthritis, ankylosing spondylitis, drug-induced subacute cutaneous lupus, sjogren's syndrome, upadacitinib.

Abbreviations:
rheumatoid arthritis RA
ankylosing spondylitis AS
drug-induced subacute cutaneous lupus DISL
disease-modifying antirheumatic drug DMARDs

Introduction

Rheumatoid arthritis (RA) and ankylosing spondylitis (AS) are the most common inflammatory rheumatic diseases. Both are characterized by chronic inflammation, joint destruction and disability, but their etiology, classic symptoms, serologic tests and imaging findings are distinct. Morning stiffness and peripheral arthritis can be found in both diseases. The genetic predisposition is different: the presence of HLA-DR4 is frequently described in patients with RA, whereas HLA-B27 is prevalent among patients with AS [1]. The coexistence of RA and AS is rare. The first case was described in 1976 [2]. The presence of rheumatoid factor (RF) is an important diagnostic marker for RA [3], while the association of anti-citrullinated protein antibodies (ACPA) increases diagnostic specificity [4]. Approximately 10-30% of patients with RA develop Sjögren's syndrome, which predisposes to a more severe disease with systemic involvement and refractoriness to treatment [5]. Sulfasalazine and tumor necrosis factor alpha (TNFα) inhibitors, including etanercept, are among the most frequently involved drugs in triggering subacute cutaneous lupus, especially in patients with RA and Sjögren's syndrome, who have a high prevalence of anti-SS-A and anti-Ro-52 antibodies [6,7,8,9]. Cutaneous manifestations appear within weeks to months after starting treatment and resolve in 74% of cases after discontinuation of therapy and administration of synthetic antimalarials [6]. The use of upadacitinib is currently being evaluated as a treatment for patients with systemic lupus erythematosus [10].

Case Presentation

A 65-year old non-smoking woman was referred to rheumatology for diagnostic evaluation after confirmation of the diagnosis of subacute cutaneous lupus in the dermatology department.

From her medical history, her symptoms began in

2002 with symmetric polyarthritis affecting the small joints of the hands and feet and she had double seropositivity (RF and ACPA). At that time, she was diagnosed with RA and started on methotrexate, with the dose gradually increased to 20 mg per week, which was well tolerated and led to a good clinical course for 10 years.

In 2012, signs of enthesitis, inflammatory low back pain and peripheral oligoarthritis appeared. Additional investigations revealed radiographic sacroiliitis and the presence of HLA-B27 antigen; thus, the diagnosis of AS with peripheral manifestations was established. Given the peripheral oligoarticular involvement, methotrexate treatment was stopped and sulfasalazine was initiated, with progressively increasing dosage up to 2000 mg/day, with a good response for 4 years.

In 2016 a new clinical finding appeared: a diffuse skin eruption arranged in plaques, for which the patient presented to dermatology. A skin biopsy was performed, showing features compatible with subacute cutaneous lupus.

At the first rheumatology consultation in our clinic in June 2016, the patient presented with a generalized rash arranged in confluent plaques, Raynaud's phenomenon and inflammatory polyarthralgia involving the knees, small joints of the hands, left elbow and left wrist. The osteoarticular clinical examination revealed thoracic kyphosis, lumbar straightening, absence of joint swelling, anteroposterior subluxations of the toes and amputation of the second toe of the right foot secondary to hammer toe deformity (Figure 1).

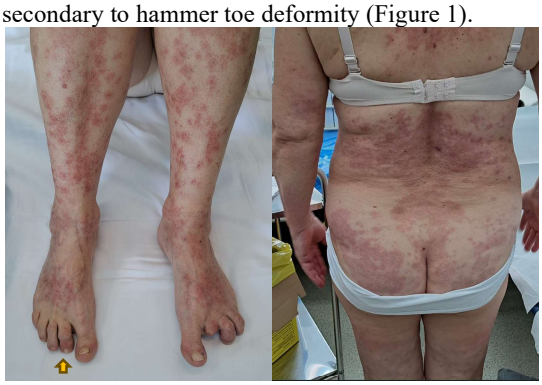
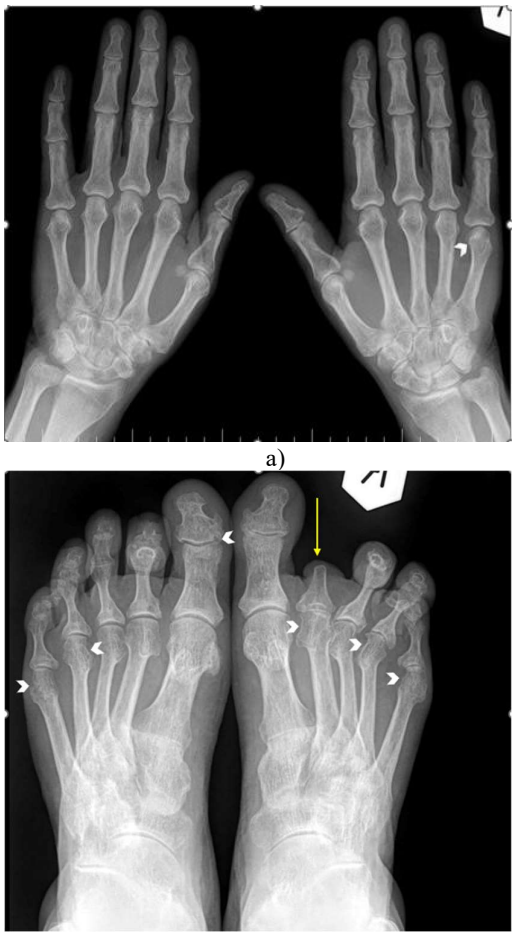


Figure 1. *Generalized rash: confluent plaques, confirmed on dermatologic biopsy as subacute cutaneous lupus erythematosus. The yellow arrow indicates the amputation of the second toe of the right foot due to changes consistent with hammer toe deformity.*

The laboratory findings were: normal complete blood count, acute phase reactants within normal limits, high-titer RF and ACPA (RF = 400.07 UI/mL, normal < 30 UI/mL; ACPA = 250 UI/mL, normal < 20 UI/mL), positive IgG antinuclear antibodies (ANA) by ELISA (92,608 U/mL, normal < 20 U/mL), negative anti-double-stranded DNA (anti-dsDNA) and anti-Smith (anti-Sm) antibodies by ELISA, extended ANA panel showing positive anti-histone antibodies, decreased complement C3 (0,75 g/L; normal: 0,89-1,87 g/L), decreased complement C4 (0,14; normal 0,16-0,38 g/L), absent serum cryoglobulins.

For RA staging, bilateral conventional X-rays of the hands and feet were performed. The feet revealed large, symmetric erosions, predominantly at the fourth and fifth metatarsophalangeal joints, joint space narrowing and diffuse demineralization (Figure 2b). The same changes are observed in the left wrist and in the third metacarpophalangeal joint of the left hand, revealing small erosions (Figure 2a).



a)

b)

Figure 2. *a) Bilateral hand X-ray (AP view): linear erosion at the level of the 5th metacarpophalangeal joint of the right hand (arrow head) b) Feet x-ray (AP view): large, symmetric erosions at the level of 5th, 4th, 2th metatarsophalangeal joints of the right foot and at the level of the 1st interphalangeal joint and the 4th and 5th metatarsophalangeal joints of the left foot (arrow head), joint space narrowing, diffuse demineralisation and amputation of the second toe of the right foot secondary to hammer toe changes (yellow arrow).*

The pelvic radiograph shows bilateral grade 3 sacroiliitis (Figure 3).

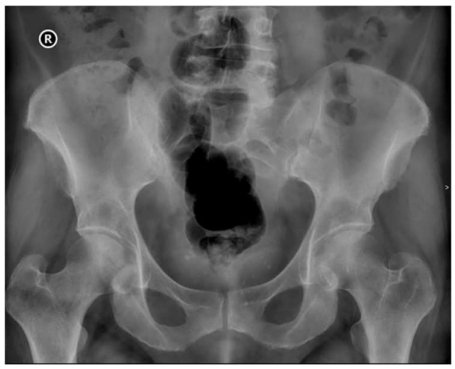


Figure 3. *Anteroposterior pelvic radiography: bilateral grade 3 sacroiliitis.*

Given the presence of Raynaud's phenomenon, videocapillaroscopy was performed, which was normal (Figure 4).

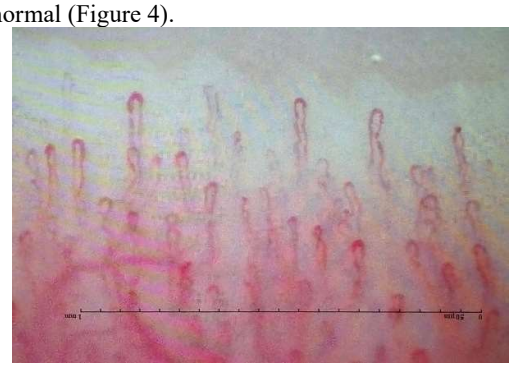


Figure 4. *Videocapillaroscopy with normal appearance*

For the cutaneous lupus lesions, treatment with glucocorticoids (prednisone 0,5 mg/kg body weight, tapered by 5 mg of prednisone per week and discontinued after 3 months) and hydroxychloroquine 400 mg/day were initiated. For the management of RA, treatment with methotrexate 20 mg per week was resumed. Under this treatment, the skin rash disappeared and the therapeutic targets for both RA (according to the DAS28-CRP) and AS (according to the ASDAS) were maintained for 2 years.

In March 2018, the diseases flared by the appearance of asymmetric oligoarthritis in the lower limbs, Achilles enthesitis and dactylitis of the second toe of the left foot, accompanied by high inflammatory markers (ESR = 32 mm/h and CRP = 15,52 mg/L) and high disease activity scores of AS (BASDAI = 6,7; ASDAS-CRP = 3,3). Accordingly, treatment was escalated to the class of biologic agents. Due to caution regarding sulfasalazine-induced cutaneous lupus, the first option was not the class of anti-tumor necrosis factor alpha agents, but rather the class of interleukin-17A blockers, specifically secukinumab, with a loading dose followed by a monthly dose of 150 mg, resulting in a rapid response and maintained remission for approximately 5 years. Methotrexate was continued for the control of RA.

In February 2023, a severe clinical flare developed in the superior cervical spine region, with severe and local inflammatory signs associated with difficult to reduce cervical anteflexion posture. Biological parameters showed high level of acute phase reactans (ESR=53 mm/H; CRP=44,87 mg/L) and very high disease activity state (BASDAI=7,5; ASDAS=4,29). A cervical spine MRI was performed, which confirmed the presence of enthesitis at of the cervical interspinous ligament, with areas of inflammation on STIR sequences at this level (Figure 5).

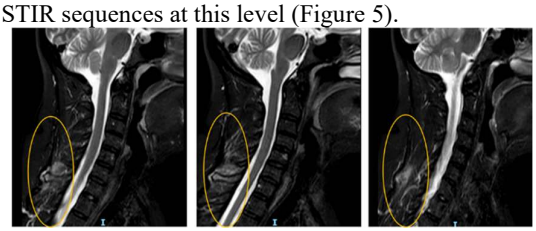


Figure 5. *MRI of the cervical spine in STIR sequence: enthesitis of the cervical interspinous ligament (yellow circles).*

The dose of secukinumab was increased to 300 mg per month. This resulted in a partial response at one month (with a decrease in the ASDAS score to 2,5), but with loss of response at five months.

In July 2023, the patient developed the same clinical symptoms as previously described, including peripheral arthritis, enthesitis and chronic cervical pain, with biological inflammatory syndrome (ESR=90 mm/H, CRP=41,24 mg/L) and very high disease activity state (BASDAI=9,5; ASDAS-CRP=5,54). The treatment was switched to etanercept biosimilar 50 mg weekly, resulting in a clinical reponse after 3 months of therapy, which was maintained over time. After 8 months of treatment, while the disease remained well controlled, the patient developed a recurrence of the cutaneous eruption. A skin biopsy reconfirmed the diagnosis of subacute cutaneous lupus (Figure 6).

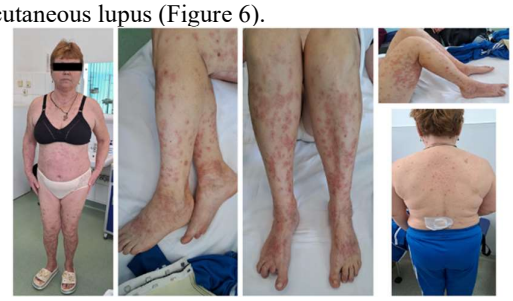


Figure 6. *Erythematous, symmetric, generalized skin lesions with sparing of the face and a tendency to coalesce (suggestive of subacute cutaneous lupus).*

Laboratory evaluation revealed an inflammatory syndrome (ESR=69 mm/h, CRP=57,83 mg/L), low complement C3 (0,76 g/L), positive anti-SS-A antibodies and positive anti-Ro-52 antibodies. Given the positivity of anti-SS-A antibodies, upon repeating the medical history, the patient reported the presence of sicca syndrome. An ultrasound of the major salivary glands was performed and showed nonspecific changes. Thus, a biopsy of the minor salivary glands was recommended, which confirmed the diagnosis of Sjogren's syndrome. Due to the onset of subacute cutaneous lupus, treatment with biosimilar etanercept

was discontinued, and topical and oral corticosteroid therapy was initiated (prednisone 0,5 mg/kg body weight for 4 weeks, followed by a gradual dose reduction and dicontinuation at 3 months), with a partial response.

In May 2024, one month after discontinuation of biological therapy, there was a flare, with severe morning stiffines of the axial skeleton, dorso-lumbar pain, associated with arthritis in the right foot, enthesitic pain in the costal region, persistent skin rash, inflammatory biological syndrome (ESR=69 mm/H, CRP=67,83 mg/L) and high disease activity state (BASDAI=7,5; ASDAS-CRP=5,48.

After analyzing the therapeutic options and shared decision with the patient, the JAK inhibitor class was selected, specifically upadacitinib 15 mg/day. A rapid clinical improvement was shortly noted, in all the clinical domains, with complete remission achieved after one month of treatment. The treatment also had a favorable effect on cutaneous lupus lesions, with complete resolution at at three months.

At 6 months, in December 2024, remission of both axial and peripheral symptoms was noted, with significant improvement in functionality (practicing aqua gym on a regular basis), absence of skin rash (Figure 7), absence of inflammatory biological syndrome (ESR=9 mm/H, CRP=2,53 mg/L), normalization of complement levels, disease activity scores consistent with inactive disease (BASDAI=0, ASDAS=0,64, DAS28-CRP=0,96) and no need for steroidal or non-steroidal anti-inflammatory drugs.

Figure 7. *Skin presentation after 3 months of upadactininb treatment*

Discussions

Given these manifestations, there is an unusual association of inflammatory rheumatic conditions: double seropositive RA, AS with peripheral involvment, Sjogren syndrome and recurrence of drug-induced subacute cutaneous lupus (DISL).

The spectrum of this associations covers distinct mechanism from autoimmune and inflammatory diseases. These conditions appeared sequentially but evolved concomitantly.

The literature describes cases of RA and AS with significant disease duration. Comparable prevalence rates (0.30%–1.50%) have been noted in the general population. Among individuals with RA and HLA-B27, 6.6% were also diagnosed with AS, while 8.3% of rheumatoid factor (RF)-positive patients had AS, versus 9.8% in controls—although these results lacked statistical significance. The likelihood of concurrent RA and AS in a single patient has been reported to range from 1 in 50,000 to 1 in 100,000, indicating that RA–Spondyloarthritis overlap is exceedingly rare. Some authors suggest that accidental detection of HLA-B27 in an RA patient does not influence the course of the underlying disease nor increase the incidence of sacroiliac joint inflammation. Similarly, the presence of RF in AS patients does not significantly raise the risk of erosive peripheral arthritis [1,2,12,13,14,15,17].

The prevalence of coexisting autoimmune diseases in patients with RA is higher than in those with osteoarthritis (OA), with AS being one of the rarest associated conditions. The highest odds ratios (ORs) comparing RA to OA were reported for AS (OR 8.0; 95% CI 7.6–8.5) and psoriatic arthritis (OR 7.8; 95% CI 7.6–8.1). Diagnosis of overlapping RA and AS is often delayed. Based on available data, this clinical combination appears to follow a more aggressive course, as most patients exhibit erosive radiographic patterns, RF positivity, axial skeleton involvement, and rheumatoid nodules with higher frequency than those with isolated diagnoses of either disease [5,7,8,16].

Regarding the association with DISL Arnaud et al. utilized the World Health Organization (WHO) pharmacovigilance database to identify 118 drugs linked to drug-induced lupus, including infliximab, adalimumab, etanercept, and sulfasalazine. The study also revealed that 42 of these drugs had not been previously associated with drug-induced lupus, suggesting an evolving spectrum of implicated agents. DISL is a distinct clinical entity, induced by medication in over one-third of cases. Sulfasalazine has been identified as a causal agent, along with antifungals (e.g., terbinafine), proton pump inhibitors (PPIs), antihypertensives (e.g., calcium channel blockers, ACE inhibitors), and TNF inhibitors [6,9,10,18,19].

While the association between Sjogren syndrome and RA is well known and relatively frequent, the association between Sjogren syndrome and AS is less common, yet possible, with at least one documented case in the literature [20].

To our knowledge—and as corroborated through Artificial Intelligence tools (ChatGPT and Open Evidence) [21]—the coexistence of all four conditions (RA, AS, DISL, and SS) in a single patient has not previously been reported. For the therapeutic management of such a complex case, all these disease entities were considered. It was decided to initiate treatment with Janus kinase inhibitors (JAK inhibitors), a drug class with demonstrated efficacy in both RA and AS, without reported associations with drug-induced lupus, and with emerging data supporting their efficacy and safety in systemic lupus erythematosus (SLE) from phase 2 clinical trials [10,21].

Conclusions

This case highlights the diagnostic and therapeutic complexity of overlapping RA and AS and Sjögren's syndrome, the risk of cutaneous adverse reactions under sulfasalazine and etanercept, as well as the need for multidisciplinary monitoring and therapeutic strategy adaptation based on the immunologic profile and clinical progression.

Patient Consent: obtained.

Conflicts of Interest: The authors declare no conflicts of interest.

Author`s contributions

writing—original draft preparation, MM, BD
clinical management of the patient—CM, BD
writing—review and editing BD, CM
final revision—CC

All authors have read and agreed to the published version of the manuscript.

References

[1] Maksymowych WP, Brown MA. Genetics of ankylosing spondylitis and rheumatoid arthritis: where are we at currently, and how do they compare? Clin Exp Rheumatol. 2009;27(4 Suppl 55):S20–S25. PMID: 19999105.

[2] Fallet GH, Mason M, Berry H, Ansell BM, Bywaters EG. Rheumatoid arthritis and ankylosing spondylitis occurring together. Br Med J. 1976;1(6013):804–7. doi:10.1136/bmj.1.6013.804. PMID: 1260352. PMCID: PMC1639374.

[3] Song YW, Kang EH. Autoantibodies in rheumatoid arthritis: rheumatoid factors and anticitrullinated protein antibodies. QJM. 2010;103(3):139–46. doi:10.1093/qjmed/hcp165. PMID: 20080813.

[4] Toes REM, van der Woude D. ACPA (anti citrullinated protein antibodies) and rheumatoid arthritis. Acta Reumatol Port. 2011;36(3):205–7. PMID: 22031362.

[5] Laroche M, Degboe Y, Constantin A. Sjögren's syndrome associated with erosive rheumatoid arthritis alters its prognosis and long term therapeutic response: a case control study. Rheumatol Int. 2023;43(2):363–6. doi:10.1007/s00296-021-05074-0. PMID: 35196458.

[6] Alniemi DT, Gutierrez A Jr, Drage LA, Wetter DA. Subacute cutaneous lupus erythematosus: clinical characteristics, disease associations, treatments, and outcomes in a series of 90 patients at Mayo Clinic, 1996–2011. Mayo Clin Proc. 2017;92(3):406–14. doi:10.1016/j.mayocp.2016.10.030. PMID: 28185656.

[7] Ramos Calsals M, Brito Zerón P, Font J. The overlap of Sjögren's syndrome with other systemic autoimmune diseases. Semin Arthritis Rheum. 2007;36(4):246–55. doi:10.1016/j.semarthrit.2006.08.007. PMID: 16996579.

[8] Theander E, Jacobsson LT. Relationship of Sjögren's syndrome to other connective tissue and autoimmune disorders. Rheum Dis Clin North Am. 2008;34(4):935–47. doi:10.1016/j.rdc.2008.08.009. PMID: 18984413.

[9] Bernacchi E, Neri R, Caproni M, Loggini B, Fabbri P, Bombardieri S. Annular subacute cutaneous lupus erythematosus lesions and polymyositis onset in a patient with primary Sjögren's syndrome: how should this unusual association be classified? Lupus. 2013;22(3):312–5. doi:10.1177/0961203312474703. PMID: 23358869.

[10] Merrill JT, Tanaka Y, D'Cruz D, et al. Efficacy and safety of upadacitinib or elsubrutinib alone or in combination for patients with systemic lupus erythematosus: a phase 2 randomized controlled trial. Arthritis Rheumatol. 2024;76(10):1518–29. doi:10.1002/art.42926. PMID: 38923871.

[11] Dundar U, Cevik H, Demirdal US, et al. Use of rituximab to treat a patient with coexistence of rheumatoid arthritis and ankylosing spondylitis: 18 months follow up. Int J Rheum Dis. 2014. doi:10.1111/1756-185X.12303. PMID: 24618052.

[12] Toussirot E, Acquaviva PC. Coexisting rheumatoid arthritis and ankylosing spondylitis: discussion of 3 cases with review of the literature. Clin Rheumatol. 1995;14(5):554–60. doi:10.1007/BF02208154. PMID: 8549095.

[13] van der Horst Bruinsma IE, Lems WF, Dijkmans BA. A systematic comparison of rheumatoid arthritis and ankylosing spondylitis. Clin Exp Rheumatol. 2009;27(4 Suppl 55):S43–S49. PMID: 19822045.

[14] Appel H, Loddenkemper C, Miossec P. Rheumatoid arthritis and ankylosing spondylitis – pathology of acute inflammation. Clin Exp Rheumatol. 2009;27(4 Suppl 55):15–19. (No PMID/DOI found.)

[15] Major P, Resnick D, Dalinka M, Kline P. Coexisting rheumatoid arthritis and ankylosing spondylitis. AJR Am J Roentgenol. 1980;134(5):1076–9. doi:10.2214/ajr.134.5.1076. PMID: 6768253.

[16] Simon TA, Kawabata H, Ray N, Baheti A, Suissa S, Esdaile JM. Prevalence of co existing autoimmune disease in rheumatoid arthritis: a cross sectional study. Adv Ther. 2017;34(11):2481–90. doi:10.1007/s12325-017-0627-3. PMID: 29074172.

[17] Flores Robles BJ, et al. Concurrence of rheumatoid arthritis and ankylosing spondylitis: analysis of seven cases and literature review. Case Rep Rheumatol. 2022;2022:8500567. doi:10.1155/2022/8500567. PMID: 36335064.

[18] Arnaud L, Mertz P, Gavand PE, Martin T, Chasset F, Tebacher Alt M, et al. Drug induced systemic lupus: revisiting the ever changing spectrum of the disease using the WHO pharmacovigilance database. Ann Rheum Dis. 2019;78(4):504–8. doi:10.1136/annrheumdis-2018-214598. PMID: 30309972.

[19] Ye W, Ding Y, Li M, Tian Z, Wang S, Liu Z. Safety assessment of sulfasalazine: a pharmacovigilance study based on FAERS database. Front Pharmacol. 2024;15:1452300. doi:10.3389/fphar.2024.1452300. PMID: 38101757.

[20] Zhao GW, Huang LF, Li D, Zeng Y. Ankylosing spondylitis coexists with rheumatoid arthritis and Sjögren's syndrome: a case report with literature review. Clin Rheumatol. 2021;40(5):2083–6. doi:10.1007/s10067-020-05350-7. PMID: 32948301.

[21] OpenAI. Response generated by ChatGPT and Open Evidence regarding case reports involving rheumatoid arthritis, spondylitis, Sjögren's syndrome, and drug induced lupus. ChatGPT. 2025 Jun 1. (No PMID/DOI).

Corresponding author

Bianca-Margareta Dumitrescu, Dr. Ion Stoia" Clinical Centre for Rheumatic Diseases, Bucharest, Romania; email: Bia1mar@yahoo.com

Received: 12.01.2025

Accepted: 28.01.2025