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Case Report

A Clinical Case of a 74-Year-Old Patient with Overlap of Rheumatoid Arthritis and Axial Spondyloarthritis

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Running title: Overlap of Rheumatoid Arthritis and Axial Spondyloarthritis

Abstract

In the past, rheumatoid arthritis and axial spondyloarthritis were considered mutually exclusive diseases because of their distinct genetic and clinical profiles. We present the case of a 74-year-old man with seropositive rheumatoid arthritis and long-standing axial spondyloarthritis, illustrating the diagnostic and therapeutic challenges associated with this rare overlap. The patient presented with symmetrical erosive-destructive polyarthritis involving joints of the upper extremities, strongly positive immunological markers, a history of chronic inflammatory low back pain beginning at approximately 35 years of age, positive HLA-B27, radiographic sacroiliitis and spondylitis with syndesmophyte formation and complete bony bridges between vertebral bodies. Given the predominant clinical manifestations, the presence of concomitant prostate carcinoma, and having in mind the urological consultation, combination therapy with methotrexate and tocilizumab was initiated, resulting in low disease activity. This case highlights the challenges in diagnosing and treating patients with two

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distinct inflammatory joint diseases and discusses the importance of individualized therapeutic strategies.

Keywords: seropositive rheumatoid arthritis, axial spondyloarthritis, HLA-B27, methotrexate, tocilizumab, synovitis, spondylitis

1. Introduction

Rheumatoid arthritis (RA) is a chronic inflammatory joint disease characterized by erosive-destructive polyarthritis involving joints of the upper extremities and positive immunological markers. The pathogenesis of RA includes autoimmune activation of B- and T-lymphocytes, formation of autoantibodies (rheumatoid factors, RF and anti-cyclic citrullinated peptide antibodies, anti-CCP), and chronic synovial inflammation leading to erosive joint changes and functional impairment [1].

Modern treatment of RA is based on the recommendations of the European Alliance of Associations for Rheumatology (EULAR) and includes conventional synthetic (csDMARDs), biologic (bDMARDs) and targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), as well as nonsteroidal anti-inflammatory drugs (NSAIDs) and glucocorticoids. The primary therapeutic goal is to achieve and maintain remission or low disease activity, assessed by validated indices such as the disease activity score (DAS28) [1]. Treatment choice depends on disease activity, structural damage progression, comorbidities, and safety profile.

Axial spondyloarthritis (axial SpA) is an immune-mediated chronic inflammatory disease characterized by chronic inflammatory low back pain with onset before 45 years of age and imaging evidence of sacroiliitis, often accompanied by extra-musculoskeletal manifestations. The primary sites of inflammation are the enthesis, sacroiliac joints, and facet joints. Clinical features include axial skeleton involvement, peripheral arthritis, enthesitis, and dactylitis [3]. The disease is characterized by new bone formation with syndesmophyte development, complete bony bridges between vertebral bodies, and progressive spinal ankylosis.

The pathogenesis of axial SpA involves genetic predisposition (particularly HLA-B27), immune mechanisms, and a local enthesis-driven inflammatory response, distinct from the synovial inflammation observed in RA [3].

Current treatment of axial SpA is based on ASAS–EULAR (2022) recommendations [4]. NSAIDs are first-line therapy for pain and stiffness.

In patients with persistently high disease activity despite optimal conventional treatment, bDMARDs are recommended, most commonly tumor necrosis factor-alpha (TNFα) inhibitors, interleukin-17 (IL-17) inhibitors, or tsDMARDs such as Janus kinase inhibitors (JAKi). To date, other biological classes, including interleukin-6 (IL-6) inhibitors, have not demonstrated clinical efficacy in axial SpA.

The therapeutic goal in both RA and axial SpA is control of inflammation, prevention of structural damage, and improvement of quality of life.

Although traditionally regarded as distinct nosological entities, rare cases of overlap syndrome between RA and axial SpA have been reported. Herein, we present the case of a 74-year-old man with seropositive RA and long-standing axial SpA. The coexistence of these two diseases in a single patient is rare and presents unique diagnostic and therapeutic challenges [5].

2. Case Presentation

A 74-year-old man was admitted to the Rheumatology Clinic of University Hospital "St. Ivan Rilski" with a three-month history of pain, swelling, and morning stiffness in the small joints of the hands, wrists, and shoulders. The pain was inflammatory in nature, most pronounced in the morning, with night pain awakening the patient. Morning stiffness lasted approximately 45 minutes.

Additionally, the patient reported the presence of chronic inflammatory back pain for approximately 40 years, with limited cervical and lumbar spine mobility. He reported no history of psoriasis, inflammatory bowel disease, acute anterior uveitis, enthesitis or dactylitis.

He had not received systemic anti-rheumatic treatment previously. He had been taking NSAIDs on demand for back and peripheral joint pain, with partial and temporary clinical efficacy. He had not been treated with targeted therapies.

In March 2021, he was diagnosed with well-differentiated prostate adenocarcinoma (Gleason score 3+3=6) and was treated with radiotherapy and hormonal therapy, currently being in remission. There was no history of allergies or family history of rheumatic disease. He had long-term occupational exposure to physical strain as a truck driver, likely contributing to misinterpretation of spinal symptoms as mechanical.

On physical examination, the patient was in good general condition with a hypersthenic body habitus, the skin was normally coloured without any

rashes. No abnormalities were detected on examination of the internal organs. Musculoskeletal examination revealed tenderness in metacarpophalangeal and wrist joints, synovitis of the left wrist, pain and limited shoulder motion, and restricted spinal mobility in all segments (Bath Ankylosing Spondylitis Metrology Index (BASMI) score 2).

Laboratory tests showed elevated CRP (55.7 mg/L) and ESR (76 mg/L). Immunology revealed strongly elevated rheumatoid factor IgM (>500 U/mL) and anti-CCP antibodies (1000 U/mL). The patient was HLA-B27 positive.

Radiographs demonstrated erosive-destructive changes in the hand joints, as well as spondylitis (syndesmophytes and complete bony bridges between vertebral bodies) and bilateral sacroiliitis stage IV. (Figures 1-3).

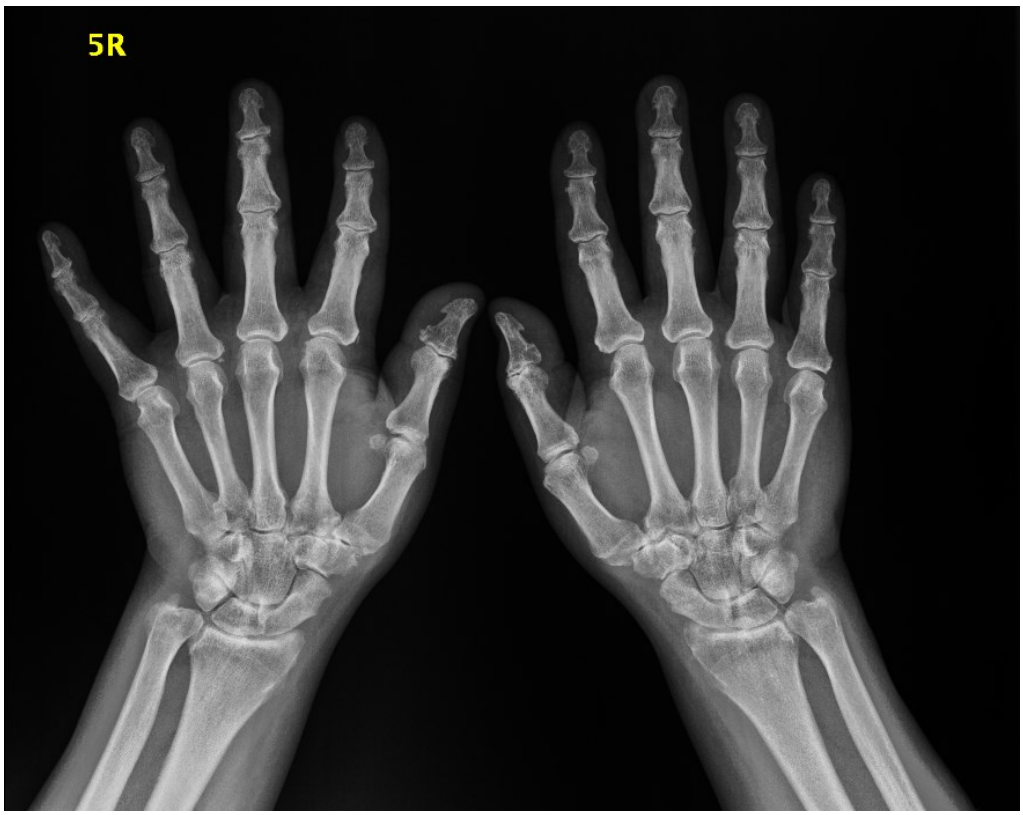


Figure 1. Radiography of wrists with palms and fingers at the time of diagnosis.

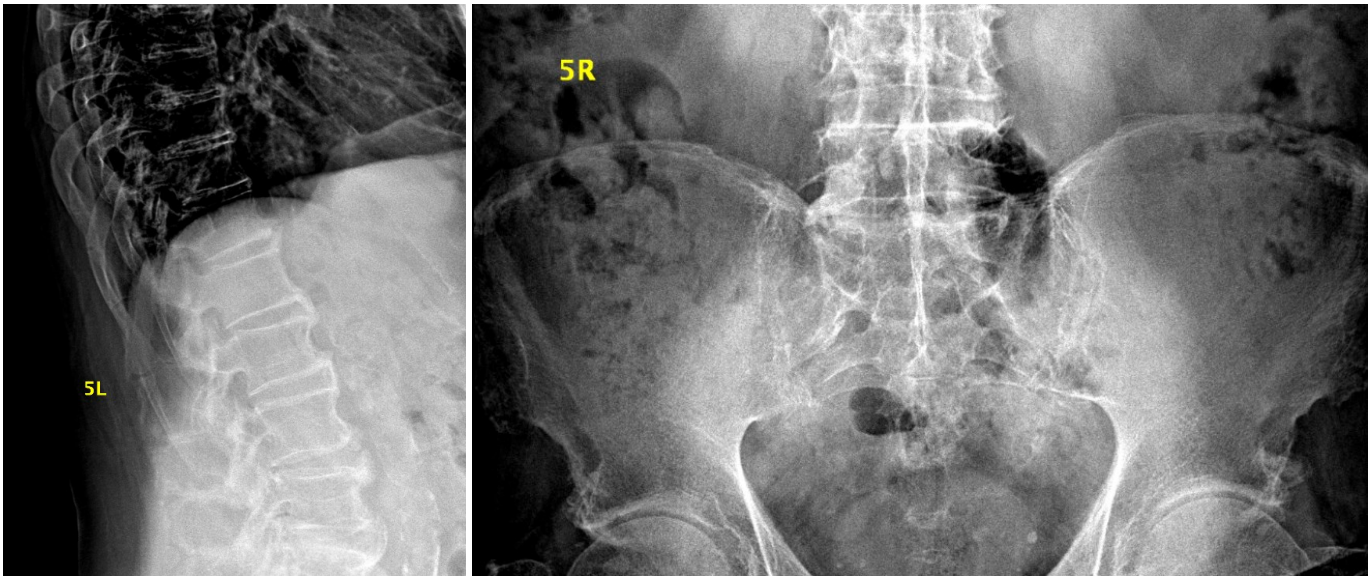


Figure 2. Lateral radiography of thoracolumbar segment of the spine and the sacroiliac joints at the time of diagnosis.



Figure 3. Computed tomography of the sacroiliac joints at the time of diagnosis.

Ultrasound confirmed bilateral synovitis in wrist and small joints of the hands – gray-scale grade II on the right and III on the left, with positive

Power Doppler (PD) signal grade I on the right and II on the left, as well as synovitis of PIP II on the right, without PD signal.

Ultrasound of shoulder joints demonstrated bilateral proliferative tenosynovitis of the long head of the biceps tendon, erosions along the humeral head contour, bilateral glenohumeral joint effusion with marked synovial hypertrophy and bilateral subacromial-subdeltoid bursitis.

The patient had very high peripheral arthritis activity with DAS using CRP (DAS28-CRP) of 6.6, an Ankylosing Spondylitis Disease Activity Score using CRP (ASDAS-CRP) of 3.9 and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) of 5.8.

A diagnosis of seropositive RA with high disease activity combined with long-standing, previously untreated radiographic axial SpA was made. Treatment was initiated with methotrexate 15 mg/week orally with folic acid supplementation and NSAIDs for axial SpA.

After 3 months, remission or low disease activity was not achieved. Despite significant improvement in back pain and stiffness, synovitis persisted in wrists and shoulders. Addition of a bDMARDs was recommended. Due to concomitant prostate carcinoma, consultation with the treating urology team advised avoiding TNFα inhibitors. Considering prevailing recommendations and limited safety data at that time, anti-TNFα therapy was not initiated.

Given the predominance of active seropositive RA, treatment with the IL-6 inhibitor tocilizumab 162 mg/week was started. JAKi were considered unsuitable due to the patient's age, the lack of specific safety data regarding JAKi use in patients with a history of carcinoma and concomitant risk factors (cardiovascular risk).

After 6 months of treatment with methotrexate 15 mg/week and tocilizumab 162 mg/week, low disease activity was achieved – chronic synovitis in shoulder joints persisted, but with improved range of motion. The patient reported significant reduction in pain and stiffness, there was no night pain and no functional deficit. Control indices of activity were calculated – DAS28-CRP 2.4, ASDAS-CRP 2.1, BASDAI 3.2. Acute-phase reactants normalized.

At 12 months, clinical remission was achieved – there was no synovitis of peripheral joints, morning stiffness was significantly reduced, there was no night pain and acute-phase markers remained within normal range. Control

indices of activity were calculated – DAS28-CRP 1.6, ASDAS-CRP 1.2, BASDAI 1.3.

At 24 months, on continued tocilizumab (162 mg/week) and reduced methotrexate (5 mg/week), the patient remained in persistent clinical remission with no radiographic progression (Fig. 4).

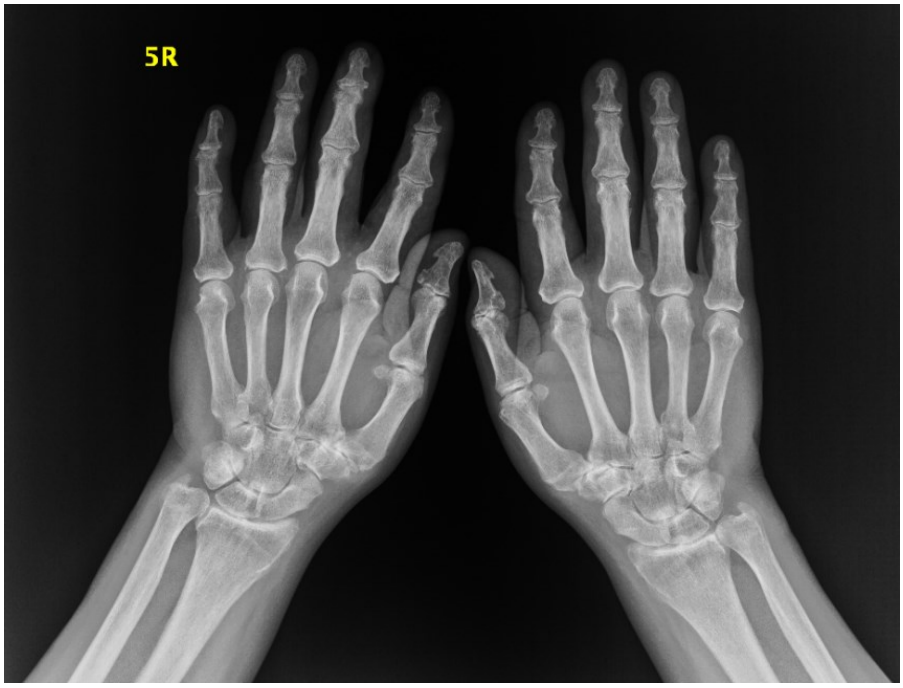


Figure 4. Radiography of wrists with palms and fingers at the 24th month of follow-up.

3. Discussion

The coexistence of seropositive RA and axial SpA is exceptionally rare. Until the mid-1990s, approximately 40–50 confirmed cases were reported, with an estimated prevalence of approximately 1:100 000 [5], although subsequent reports suggest wide variability, ranging from 1:50 000 to 1:2 000 000 [6]. This reflects the lack of population studies and the fact that the available data originate predominantly from individual clinical cases and small studies.

RA and axial SpA have distinct pathogenetic mechanisms, resulting in different clinical manifestations and requiring a disease-specific therapeutic approach. In RA, inflammation is primarily synovial, leading to synovitis, erosions and joint deformities. In contrast, axial SpA is characterized predominantly by enthesitis and perifibrocartilaginous osteitis. This distinction is particularly relevant in overlap cases such as the

present one, in which both synovial inflammation typical of RA and enthesopathic inflammation characteristic of axial SpA were observed.

An additional important aspect of this case is the concomitant prostate carcinoma. In routine clinical practice this represents a frequent therapeutic challenge. In this case, close collaboration with a urologist is essential to minimize potential treatment-related risks. Therapeutic decisions must therefore be carefully individualized, balancing rheumatic disease activity with oncological considerations and current recommendations. More recent EULAR recommendations and expert opinions regarding the initiation of biological therapy in patients with inflammatory joint diseases and a history of malignancy suggest that TNFα inhibitors may be an appropriate therapeutic option in selected patients [2]. In the present case, however, modification of the therapeutic strategy was not required due to the achievement of low disease activity and a stable clinical condition.

This case also illustrates the diagnostic challenges in such overlap. The presence of erosive-destructive polyarthritis involving the small joints of the hands, together with strongly positive anti-CCP antibodies and RF fulfilled the classification criteria for seropositive RA with high disease activity (DAS28 6.6). Additionally, a history of chronic inflammatory low back pain with onset before the age of 45 years, reduced spinal mobility, HLA-B27 positivity, and radiographic evidence of bilateral grade IV sacroiliitis, syndesmophytes, and complete vertebral bony bridging fulfilled the ASAS criteria for radiographic axial SpA [4].

On the other hand, the limited cervical spine mobility raised an important differential-diagnostic consideration. In patients with seropositive RA, atlantoaxial joint involvement must always be considered, as it is a well-recognized complication, particularly in long-standing or highly active disease [7]. Careful clinical and imaging evaluation is therefore required to differentiate ankylosis related to axial SpA from potential RA-associated cervical instability.

The therapeutic approach in patients with overlapping RA and axial SpA requires an individualized strategy, based on predominant clinical manifestations, disease stage and comorbidities [12]. In the present case priority was given to controlling the high RA activity. Methotrexate was initiated as a conventional synthetic DMARD in accordance with international RA treatment recommendations [13]. Anti-TNFα therapy was not implemented due to the concomitant oncological disease and the

consultation by the attending urology team, taking into account the limited safety data available at that time regarding TNFα inhibitors in patients with prostate carcinoma. At the time of therapeutic decision-making (2022–2023) no recommendations endorsed the use of TNFα inhibitors as an appropriate treatment option in patients with inflammatory arthritis and a history of malignancy. The existing EULAR and ASAS–EULAR recommendations emphasized individual risk assessment and a multidisciplinary approach. In clinical practice caution generally predominated regarding the use of TNFα inhibitors in patients with a recent history of malignancy [2]. More recent 2024 EULAR "points to consider" support the use of TNFα inhibitors as a potential therapeutic option in selected patients with a history of solid tumors [11].

The potential use of JAKi was also considered, as this therapeutic class is recommended for both RA and axial SpA. However, in this case the patient was 74 years old, had concomitant oncological disease and increased cardiovascular risk. Available data indicating a higher incidence of cardiovascular events and venous thromboembolism in patients over 65 years of age treated with JAKi led to avoidance of this therapeutic class [8].

Tocilizumab was chosen due to marked systemic inflammation and persistent high RA activity despite methotrexate therapy. Although IL-6 inhibitors have not shown efficacy in axial SpA [9], axial disease in this patient was longstanding with established structural damage, shifting the primary therapeutic focus to peripheral arthritis. Combination therapy with methotrexate and tocilizumab resulted in low disease activity at 6 months and clinical remission at 12 months.

Similar cases of overlap between seropositive RA and axial SpA have been reported in the literature, however, available data remain limited to individual case reports or small series. The publications highlight the complexity and the absence of established therapeutic algorithms, as these two conditions have traditionally been regarded as mutually exclusive entities, often leading to delayed diagnosis [5,6,14]. Combined biological therapy (e.g., anti-IL-17 plus anti-IL-6) could theoretically provide more control of both diseases, however, no randomized trials have demonstrated its safety or efficacy, and the risk of infection remains a major limitation [10].

4. Conclusions

The coexistence of RA and axial SpA is rare but clinically meaningful. The presence of classic seropositive RA does not exclude axial SpA in patients with a history of longstanding inflammatory back pain.

Treatment should be individualized, based on the predominant clinical manifestations, with the aims of achieving sustained remission, preventing radiographic progression, and optimizing quality of life. Early recognition and personalized therapy can significantly improve clinical outcomes and overall quality of life in patients with rheumatic diseases.

Author Contributions

Conceptualization: G.K.; Methodology: G.K., V.T.; Formal analysis: V.T., P.E.; Investigation: G.K., V.T, P.E., M.I.; Writing—original draft: G.K., V.T.; Writing—review & editing: G.K., V.T, P.E., M.I.

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Declaration

The case report was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement

Informed consent was obtained from all subjects involved in the study.

Data Availability Statement

The data presented in this study are available on reasonable request from the corresponding author.

Conflicts of Interest

The authors declare no conflict of interest.

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КЛИНИЧЕН СЛУЧАЙ НА 74-ГОДИШЕН ПАЦИЕНТ С ПРИПОКРИВАНЕ НА РЕВМАТОИДЕН АРТРИТ И АКСИАЛЕН СПОНДИЛОАРТРИТ

Резюме

В миналото, ревматоидният артрит и аксиалният спондилоартрит са се считали за взаимно изключващи се заболявания поради различните им генетични и клинични профили. Представяме клиничен случай на 74-годишен мъж със серопозитивен ревматоиден артрит и дългогодишен аксиален спондилоартрит, който илюстрира диагностичните и терапевтичните предизвикателства, свързани с това рядко припокриване. Пациентът се представя с клинична картина на симетричен ерозивно-деструктивен полиартрит, ангажиращ ставите на ръцете, със силно положителни имунологични маркери, анамнеза за хронична възпалителна болка ниско в гърба (low back pain) възникнала около 35-годишна възраст, положителен HLA-B27 и рентгенографски сакроилиит и спондилит с формиране на синдесмофити и пълни костни мостове между прешленните тела. С оглед водещата симптоматика, отчитайки наличието на придружаващ карцином на простатата и проведената консултация с уролог, пациентът е лекуван с комбинация от метотрексат и тоцилизумаб, с постигане на ниска болестна активност. Представеният случай подчертава предизвикателствата при диагностицирането и лечението на пациенти с две различни възпалителни ставни заболявания и обсъжда значението на индивидуализираните терапевтични стратегии.

Ключови думи: серопозитивен ревматоиден артрит, аксиален спондилоартрит, HLA-B27, метотрексат, тоцилизумаб, синовит, спондилит