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Complex Overlap Syndrome of Rheumatoid Arthritis and Systemic Lupus Erythematosus: A Therapeutic Breakthrough with Azathioprine

Rana Dwai^{1*}

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ABSTRACT

This case study explores the complex nature of coexisting autoimmune diseases, which is most effectively demonstrated by the coexistence of rheumatoid Arthritis (RA) and systemic lupus erythematosus (SLE), also referred to as “rhumus syndrome.” A comprehensive evaluation of a 28-year-old woman with joint discomfort, morning stiffness, and increased C-reactive protein (CRP) values was conducted. Anti-cyclic citrullinated peptide (CCP), antinuclear antibodies (ANA), and other pertinent serological indicators were examined in the laboratory. The patient’s medical background, prior therapies, and family history were considered to create an individual therapy strategy. The patient’s symptoms remained despite a long history of disease-modifying anti-rheumatic medication (DMARD) use. Positive outcomes for anti-CCP, anti-ANA, and anti-double-stranded DNA (anti-dsDNA) antibodies provide light on the overlap of multiple autoimmune diseases. The diagnostic difficulty was increased when autoimmune neutropenia was diagnosed with a bone marrow biopsy. Once azathioprine therapy was started, symptoms significantly and quickly improved within a month. Azathioprine was found to be successful in the remission of the disease. Azathioprine therapy’s critical role in treating overlapping autoimmune illnesses emphasizes the necessity for individualized and advanced testing and treatment. Targeted immunosuppressive medicines have the potential to make significant advances and enhance patient care and results.

INTRODUCTION

Approximately 200 medical conditions come under the umbrella of Rheumatic disease. Multisystem autoimmune diseases primarily affect the bones, muscles, and joints and are characterized by immunological instability (Susmita *et al.*, 2022). Clinically, they are distinguished by varied degrees of impairment, pain, stiffness, inflammation, and deformity (Susmita *et al.*, 2022). Rheumatoid Arthritis (RA) and systemic lupus erythematosus (SLE) are both autoimmune diseases in which the immune system goes against the body’s immune system, attacking the healthy tissues. The attack causes inflammation in different affected areas of the body. Causes joint pain, joint swelling, and joint tenderness. Several patients with autoimmune diseases like rheumatoid arthritis are said to have an overlapping condition of another autoimmune disease called systemic lupus erythematosus. SLE and RA are together called Rhupus. Rhupus was first discovered about 50 years ago by peter schur. The overlapping syndrome of Rheumatoid Arthritis and systemic lupus erythematosus represents a crucial clinical varied treatment. It is a rare disorder and prevails in only 1%-2% of patients with RA (Kondo *et al.*, 2020).

Rheumatoid Arthritis is a chronic autoimmune inflammatory disease that causes inflammation in primary synovial joints leading to disrupted joint structure and function (Radu & Bungau, 2021). Several autoimmune rheumatic disorders include systemic lupus erythematosus (SLE), Sjögren’s syndrome, adult-

onset scleroderma, spondylarthritis, psoriatic arthritis, and polymyositis (Radu & Bungau, 2021). The disease process involves the activation of immune cells, including T cells and B cells, building up the production of antibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (anti-CCP) antibodies (Rocha *et al.*, 2019). RF and Anti-CCP are also diagnostic serological markers for the disease. The distinctive feature of RA is synovial hyperplasia which contributes to cartilage and bone destruction. Leading to the characteristic destructive changes observed in affected joints (Xin *et al.*, 2021). Rheumatoid Arthritis (RA) has an unidentified origin. However, genetic, environmental, and serological variables contribute to the development of the condition. It is reported that 50–60% of RA susceptibility is attributed to smoking, a well-known environmental cause (Rocha *et al.*, 2019).

On the other hand, systemic lupus erythematosus is a complicated autoimmune condition with a wide range of autoantibodies and diverse symptoms that affect several organ systems. The formation of a wide range of autoantibodies, including anti-nuclear antibodies (ANA) and anti-double-stranded DNA antibodies (anti-dsDNA), is the defining feature of SLE. Skin rashes, joint discomfort, serositis, renal involvement, hematological abnormalities, and neurological signs are all possible clinical presentations of SLE (Lou *et al.*, 2022). The variability of the illness makes it difficult to diagnose and treat SLE since patients can present with

¹ Mediclinic hospital Al Jowhara, Al-Ain, United Arab Emirates

* Corresponding author’s e-mail: RanaDwai15@outlook.com

various symptoms that change over time. However, to treat systemic lupus erythematosus (SLE), it is advised to determine the severity of the illness, organ damage, and implications. According to the Hahn treatment plan, a mixture of immunosuppressive medications and steroids should be delivered via hydroxychloroquine. However, this method is advised in serious case instances (Tanaka, 2020). SLE occurrence varies worldwide, with North America having high rates, Africa low, and Australia lowest. The disease outcome and treatment depend on age, gender, and ethnicity. It is reported that more women are affected due to environmental and genetic factors, with severe impact on men, mainly found in females aged 15-44, affecting pregnancy and hormones (Ameer *et al.*, 2022).

Joint inflammation and involvement of several organs are features of the complicated inflammatory disease rhus syndrome. It necessitates a strategic strategy that blends RA and SLE properties. Therapeutic strategies include disease-modifying anti-rheumatic medications (DMARDs) to reduce joint inflammation and immunological dysregulation. The common DMARDs used conventionally are methotrexate, leflunomide, hydroxychloroquine and sulfasalazine (Benjamin *et al.*, 2018). The immune response is modulated significantly by immunosuppressive substances, both conventional and biological. Biological agents commonly used to treat RA are infliximab, adalimumab, etanercept, rituximab, abatacept, tocilizumab and tofacitinib (Benjamin *et al.*, 2018).

The key inflammatory pathways are disrupted by DMARDs using various mechanisms. For instance, methotrexate causes the release of adenosine, inhibits neutrophil adherence, blocks the synthesis of leukotriene B₄, and lowers IL-1 production. Other substances, such as leflunomide, which inhibits TLR9, Sulfasalazine, and hydroxychloroquine (Aletaha & Smolen, 2018). Contrarily, biological drugs play particular roles, interfering with cytokine function, impeding T-cell activation, and removing or blocking substances that stimulate B-cell activity (Oo *et al.*, 2018).

LITERATURE REVIEW

A study conducted on 105 rhus patients contributes to understanding the disease. The prevalence, clinical traits, and serological profiles of rhus individuals with both SLE and RA were investigated in the study. 10 (9.7%) of the 103 consecutive SLE patients were diagnosed with rhus. Patients with RA had decreased renal involvement, but there were no differences in neuropsychiatric, cutaneous, hematological, or serositis involvement. They did not differ from RA patients but had higher CRP positive and ESR levels. Pathological findings were seen during ultrasound exams, with hands scoring higher. Compared to SLE and RA patients, rhus patients had a larger cumulative burden (Tani *et al.*, 2013).

In a cross-sectional study, Researchers examined the clinical and immunological features of rhus patients and contrasted them with those who had SLE and RA. 200

individuals participated; 80 had SLE and RA, and 40 had rhus. Skin concerns, blood-related disorders, and joint problems were the prominent complaints. Those with rhus experienced joint symptoms resembling those of RA; however, renal involvement was less common (10%) than in those with SLE (25%). While 96.3% of patients with SLE and 92.5% of rhus patients satisfied the 2019 EULAR/ACR SLE criteria, there were no appreciable differences in the proportion of patients in either group who did. The study recommends a novel classification strategy to pinpoint overlapping autoimmune disease groups (Frade-Sosa *et al.*, 2020).

In another investigation, the treatment of RA with etanercept (ETN) and methotrexate (MTX) was examined. They aimed to determine whether these drugs could function without corticosteroids. 20 rhus patients who had never received corticosteroids or other similar medications were the subject of their study. Together with receiving MTX and ETN, these patients underwent a 24-week observation period. After administering ETN and MTX for 24 weeks, the patient's joint pain, disease activity, and other symptoms significantly improved. Although there were a few mild side effects, including infections and rashes, the medication was largely safe. This shows that treating rhus with ETN and MTX may be a successful option (Yang *et al.*, 2018). In a case study, three individuals with RA and SLE, a complex overlap of RA and SLE, are examined for their clinical and serological traits. All patients had high titers, positive anti-CCP, positive rheumatoid factor, and positive anti-nuclear and anti-dsDNA antibodies.

Additionally, several patients were found to have certain autoantibodies, such as anti-SSA and anti-Sm. Despite the difficulty of rhus syndrome, all three patients who received methotrexate, folic acid, and hydroxychloroquine treatment experienced clinical remission. In addition to highlighting the value of awareness and watchful clinical practice, the paper underlines the significance of early diagnosis and appropriate treatment (Devrimsel & Serdaroglu Beyazal, 2018). In another study, biologic disease-modifying antirheumatic medications (bDMARDs) were used to treat RA and SLE. There were 16 cases found, with rheumatoid arthritis succeeding before rhus and joint problems. Ten individuals needed bDMARDs, with abatacept occasionally being successful. With persistent responses in six patients, rituximab was frequently prescribed and extremely effective. The study emphasizes the possibility of specialized biologic therapies to treat difficult rhus cases (Rottenberg *et al.*, 2022).

These investigations collectively advance the knowledge of the complex SLE and RA comorbidity known as rhus syndrome. They provided information on the prevalence, clinical characteristics, serological profiles, and available treatments for people with rhus. The findings underline the unique immunological features of rhus, its peculiar clinical course, and the difficulties separating it from specific SLE or RA cases. The studies emphasize the value of early detection, individualized

treatment plans, and the potential effectiveness of biological medicines for treating rhus cases that are resistant to conventional treatments.

Case Presentation

In this case, a 28 years old woman was admitted to the hospital with a concern about pain in her hand joints and morning stiffness. It was advised to run a Laboratory analysis of a full blood test. The laboratory test results depicted elevated C-Reactive Protein (CRP) levels, Anti-cyclic citrullinated peptide (CCP) came to be positive, Rheumatoid Factor (RF) came to be negative, Antinuclear antibody (ANA) negative, low white blood cell count, and it was found that in family history her sister had lupus. Initially diagnosed with Rheumatoid arthritis, the patient's disease course later revealed an overlapping condition of Rheumatoid arthritis with systemic lupus erythematosus. The patient was admitted immediately and advised to give hydroxychloroquine and prednisolone intermittently. The patient's symptoms remained after intermittent therapy with hydroxychloroquine, prednisolone, and other disease-modifying anti-rheumatic drugs (DMARDs), along with a decline in white blood cell (WBC) counts.

Treatment History

The patient had an extensive history of DMARD usage, including methotrexate, cimzia, sulfasalazine, humira, and enbrel. Several treatments were discontinued due to adverse effects such as ecchymosis, headache, and recurrent upper respiratory infections. The patient's sister had a history of lupus, further complicating the diagnosis.

Diagnostic Workup

Unlike previous tests that yielded negative results, investigations revealed positive ANA and anti-dsDNA antibodies. A bone marrow biopsy indicated autoimmune neutropenia secondary to rheumatic disease. The patient's lupus-like symptoms, photosensitivity, malar rash, and persistent low WBC count posed a diagnostic challenge.

Treatment Breakthrough

With limited treatment options and considering the patient's complex presentation, Azathioprine was initiated after confirming normal Thiopurine methyltransferase enzyme levels. Remarkably, the patient reported a significant improvement in joint pain, morning stiffness, and other symptoms within one month of initiating azathioprine therapy.

Follow-Up and Outcome

After one month of azathioprine therapy, the patient remained free from joint pain and exhibited no significant complaints. Notably, the patient tolerated Azathioprine well, with no observed adverse effects.

RESULTS

The results of this case report demonstrate the challenging nature of managing a patient with overlapping features of rheumatoid arthritis and systemic lupus erythematosus, also referred to as rhus syndrome. A 28-year-old RA patient reported frequent upper respiratory infections, morning stiffness, and joint discomfort. Her symptoms remained, and her white blood cell counts declined despite therapies like DMARDs and biologics. Positive results from anti-CCP, anti-ANA, and anti-dsDNA antibody tests highlighted the complexity of coexisting autoimmune diseases. Clinical information and a low WBC count in the patient led to suspicions of autoimmune neutropenia owing to rheumatic illness. After starting azathioprine therapy within a month, the patient showed considerable improvement, suggesting the drug may effectively treat overlapping autoimmune disorders like "rhus." The laboratory analysis conducted during the initial diagnosis of Rheumatoid arthritis, prior to the initiation of treatment, is presented in Table 1. To navigate the diagnostic and therapeutic difficulties brought on by overlap syndromes, this case emphasizes the significance of considering various treatment modalities and the need for individualized, special care.

Table 1: Initial Serological Marker Analysis for Rheumatoid Arthritis Diagnosis

Test	Results	Reference range
Anti-CCP	> 195 U/ml	0-5 U/ml
Rheumatoid Factor (RF)	< 21	Negative < 30
White blood cell count (WBC)	3.2	4-10 1000/ μ L
ANA screen	0.5	Negative < 1.5
P-ANCA (MPO)	0.6 U/ml	Normal < 5
c-ANCA (PR3)	1.3 U/ml	Normal < 5
DNA, Double-Stranded Antibodies	1.5	Negative < 20

The table displays laboratory findings from various diagnostic tests, giving important details on the patient's autoimmune condition. The absence of significant rheumatoid factor antibodies indicates that the patient's Rheumatoid Arthritis (RA) might not be primarily triggered by this specific antibody. However, the

presence of elevated anti-CCP antibodies, coupled with the patient's symptoms, suggests a consideration for diagnosing Rheumatoid Arthritis. (RA). A lower white blood cell count (WBC) and an ANA screen indicate a comparatively low number of antinuclear antibodies. Results from P-ANCA and c-ANCA are within the usual

Table 2: Serological and Diagnostic Markers After Treatment for Overlapping Syndrome (Results and Reference Ranges)

Test	Results	Reference Range Limit
White Blood Cell Count (WBC)	3.3	4-10 1000/ μ L
ANA (Antinuclear Antibody)	Positive	Negative
Method	IF	
DNA, Double-Stranded Antibodies	33.8	Negative < 20
ANA Titer (Fluorescence)	> 1:1280	Negative < 1:80
Creatinine	53.8 μ mol/L	44.2-88.4
CRP (C reactive protein)	18.4 mg/L	0-5
ESR (Erythrocyte Sedimentation Rate)	41 mm/hr	2-39
Ferritin	124 ng/ml	30-120
Bone Marrow Biopsy	Autoimmune Neutropenia Secondary to Rheumatic Disease	
Chest X-Ray	Normal	
Urine Analysis		
Leukocytes	11-20 cells/HPF	Ref Range 0-5
RBC (Red Blood Cells)	0-2 cells/HPF	Ref Range 0-2
Cast	NIL	
Protein	Negative	
Thiopurine Methyltransferase Activity	123	Ref 100-200

reference limits, showing that these antibodies are not present in excess amounts. Compared to the reference range of 20, DNA double-stranded antibodies, frequently linked to systemic lupus erythematosus (SLE), are higher. The results for these serological markers, observed after the patient did not respond to treatment and indicating the presence of an overlapping syndrome, are presented in Table 2 as provided above.

The patient's autoimmune condition is complex and involves various physiological, immunological, and diagnostic aspects. The patient's WBC count 3.3 indicates leukopenia, which could be associated with immune system dysregulation. Positive ANA results indicate an autoimmune process with elevated levels of DNA, double-stranded antibodies, and ANA titers. Kidney function and inflammation markers are also investigated with normal creatinine levels and high CRP and ESR levels, Ferritin levels are also elevated, indicating increased iron stores and inflammation. Bone marrow biopsy results indicate autoimmune neutropenia, while chest X-rays show normal lung involvement. Urine analysis shows potential kidney involvement with elevated leukocytes and normal red blood cells, other than this, proteinuria and casts are favorable indicators, suggesting no significant structural kidney damage or protein loss through urine. Thiopurine Methyltransferase (TPMT) activity levels are within an expected range. Azathioprine treatment is an immunosuppressive medication used in autoimmune diseases to suppress the overactive immune response responsible for inflammation and tissue damage. It is often chosen when other treatment options have proven insufficient or caused adverse effects. The patient's complex presentation and limited treatment

options align with the choice of Azathioprine, as it may provide a broader immunosuppressive effect targeting rheumatoid Arthritis (RA) and lupus-like components.

DISCUSSION

Test results align with the patient's complex autoimmune presentation, including anti-dsDNA antibodies, elevated inflammation markers, autoimmune neutropenia, and lupus-like symptoms. Azathioprine's immunosuppressive action could help modulate the autoimmune response, leading to an improvement in lupus-related symptoms. The patient reports significant improvement in joint pain, morning stiffness, and other symptoms within one month of initiating azathioprine therapy, corroborating the connection between treatment and test results. The observed symptom improvement reflects the medication's positive impact on immune dysregulation and inflammation. Overall, the choice to initiate Azathioprine aligns well with the patient's complex autoimmune presentation, highlighting the personalized and targeted nature of the therapeutic approach.

RA and SLE can significantly affect patients' quality of life and health-related quality of life. Patients with SLE have a better chance of survival than in the past, but they still experience a low quality of life (Elera-Fitzcarrald *et al.*, 2018). Patients with SLE often have ongoing symptoms that worsen their quality of life. A study involving 104 women with SLE found that factors such as tiredness, feeling down, body image, and disease activity significantly impact patients' feelings about life quality. The study found that emotional well-being, especially when the disease is active, is crucial for improving life quality. It is essential to help patients with emotional well-being, body

image, and emotional well-being to improve their well-being (Pereira *et al.*, 2020). In another study, researchers examined the impact of belimumab and rituximab treatments on the quality of life of patients with SLE. Some patients initially experienced lower quality of life, but after a year, they experienced better physical and mental health. After three months, they experienced better mental and physical health (Parodis *et al.*, 2019). This study implied that quality of life could improve once the patient is administered proper modified treatment.

Much like SLE, RA can cause serious problems like joint pain and difficulty moving, renal dysfunctionality and stiffness which can affect a person's life. A cross-sectional study examined the impact of RA on quality of life using questionnaires. Results showed that RA patients had similar quality of life as healthy individuals in some areas. However, more pain was linked to worse social interactions, general health, and physical ability. Those with worse overall health also had more physical problems and pain. The study suggests better pain management and improved mobility and interaction are crucial for RA patients (Martinec *et al.*, 2019). The chronic autoimmune disease RA mostly affects the joints and can be painful and disabling. Another study examined the impact of RA on patients' quality of life. The study took 464 Thai patients with RA, mostly females aged 59 or older and found that disease activity and psychological health impacted patient feelings. Severe disease and emotional suffering led to lower quality of life, making this knowledge crucial for improved treatment and management (Katchamart *et al.*, 2019). It is also reported that people with RA cannot sleep properly due to severe joint pain and discomfort. Hence, sleep loss dysregulates bodily functions leading to decreased quality of life (Grabovac *et al.*, 2018).

Considering all these factors that affect the quality of life of SLE and RA patients, it is crucial to determine the management of these factors. Rhupus syndrome treatment addresses joint inflammation and autoimmune and systemic manifestations in RA and SLE (Frazzei *et al.*, 2022). Common management techniques include medication, such as Disease-Modifying Antirheumatic Drugs (DMARDs), biologic DMARDs, corticosteroids, pain and symptom management, physical therapy, immunosuppressive therapy, and hydroxychloroquine (Srivastava *et al.*, 2019). Medications include Disease-Modifying Antirheumatic Drugs (DMARDs), which control joint inflammation and slow joint damage progression. Biologic DMARDs target immune system parts to reduce inflammation, while corticosteroids provide quick relief. Pain and symptom management involves NSAIDs, analgesics, physical therapy, immunosuppressive therapy, and hydroxychloroquine (Guo *et al.*, 2018). Lifestyle modifications include a healthy diet, regular exercise, stress management, regular medical monitoring, and an individualized approach.

The findings from our case reports align with these management techniques to improve the quality of life and remission of the disease. The case report highlights

the complexity of managing rhupus syndrome, with the patient experiencing overlapping features of RA and SLE. This highlights the need for an individualized treatment approach. Laboratory analysis revealed antibodies associated with RA and SLE, highlighting the diagnostic challenges of overlap syndromes and the need for comprehensive serological marker analysis. Autoimmune neutropenia was suspected, leading to the initiation of azathioprine therapy. This strategy addresses overlapping features and complications in autoimmune diseases like rhupus. Ongoing monitoring and follow-up are crucial, as are regular medical evaluations to adjust treatment based on disease activity and patient progress. Despite therapies like DMARDs and biologics, the challenges faced in managing the patient's symptoms highlight the complexity of rhupus syndrome. This complexity aligns with the need for a multifaceted treatment strategy that considers the diverse aspects of the disease and the potential for overlapping manifestations. The case report provides a real-world example that reinforces the management techniques and considerations discussed in the context of rhupus syndrome.

CONCLUSION

This case emphasizes the difficulty in diagnosing and treating overlapping autoimmune diseases like rhupus syndrome. Accurate diagnosis and treatment are made more difficult by the convergence of RA and SLE symptoms. To solve the case of overlapping autoimmune manifestations, an integrative strategy is required. The patient's reaction to azathioprine therapy indicates a potential advancement in treating overlapping rheumatoid arthritis and lupus. This accomplishment emphasizes the significance of modifying treatments to target the immunological causes of these illnesses. This case can inspire medical professionals and academics to investigate advanced therapeutic approaches and recognize the complexity of related autoimmune diseases.

Strengths and Implications

This research will significantly impact clinical practice. Re-evaluation is essential when RA patients don't respond well to medication since they could risk acquiring lupus or other autoimmune illnesses. Achieving disease remission, improving patients' quality of life, and ensuring patient safety all depend on prompt action. The findings of this study may help other medical professionals identify autoimmune conditions that need special care. This study also emphasizes the importance of ongoing monitoring in patients with autoimmune disorders, such as RA, to quickly detect the onset of lupus or other autoimmune conditions. This research has the potential to significantly affect patient outcomes and general well-being by providing appropriate treatment methods for disease remission and enhanced quality of life.

Informed Consent

Informed consent was taken from the patient in order to

carry on the study.

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Conflict of Interest

The author declares no Conflict of Interest.

Author's Contribution

The author contributed in the design, experimentation, writing, data generation, editing, proof read and verification of the study.

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