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CASE REPORT

Navigating Rhupus Complexity

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Abstract

The term 'Rhupus,' introduced by Peter Schur in 1971, describes patients meeting criteria for both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). Rhupus (RhS) is a rare syndrome, and approximately 60 cases have been described in the literature to date. The challenges in diagnosing this disease stem from the lack of well-defined clinical criteria. In this case, we present a 42-year-old female patient with overlap syndrome of RA and SLE (RhS) who developed inflammatory arthritis, swelling in her bilateral wrists, severe malar rash, oral ulcers and alopecia, anemia and thrombocytopenia during follow-up. Upon arrival, the patient's laboratory values were as follows: erythrocyte sedimentation rate: 61 mm/hour (normal value: 0-20), hemoglobin: 8.3 g/dL (12-16), platelet count: 112.103/µL (150-450.103/µL). The purpose of documenting this case is to share our own experience with a syndrome that is quite rare and has the potential to cause confusion in the daily practice of clinicians.

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Introduction

Autoimmunity is one of the top ten causes of mortality and morbidity in young women, occurring at similar rates in different parts of the world. Approximately 20% of patients with a history of autoimmunity may develop additional autoimmune diseases, leading to overlapping conditions.[1] The term 'Rhupus,' introduced by Peter Schur in 1971, describes patients meeting criteria for both rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE).[2] Rhupus (RhS) is a rare syndrome, and approximately 60 cases have been described in the literature to date. The challenges in diagnosing this disease stem from the absence of well-defined clinical criteria.[3] Generally, Rhupus is known for having less internal organ involvement than SLE. It is a neglected topic that arises concurrently with the development of RA and SLE, respectively. It is estimated that the Rhupus syndrome develops in 0.05% to 2% of patients with RA or SLE.[4] Although the cause of this disease has not been fully elucidated, the literature suggests that various genetic, environmental and immunological factors may play a role.[1]

Some authors have described Rhupus syndrome as a subtype of SLE accompanied by severe arthritis. In the course of lupus, three types of joint involvement can be observed: non-erosive arthropathy (the most common, known as Jaccoud), erosive symmetric polyarthritis (Rhupus syndrome), and mild deforming arthropathy.[5] However, the widely accepted perspective is that this involves deforming, symmetrical, erosive polyarthritis accompanied by the symptoms and signs of SLE. It is characterized by the presence of specific antibodies crucial for diagnosis, including Anti-Smith (anti-Sm), Anti-double stranded DNA (anti-ds DNA), and anti-cyclic citrullinated peptide (anti-CCP).[6]

Case

In this case, we present a 42-year-old female patient with overlap syndrome of RA and SLE (RhS) who developed anemia and thrombocytopenia during follow-up. The purpose of documenting this case is to share our own experience with a syndrome that is quite rare and has the potential to cause confusion in the daily practice of clinicians. A 42-year-old female patient has been under our rheumatology outpatient clinic's follow-up since 2019, diagnosed with seropositive rheumatoid arthritis. The diagnosis was supported by clinical evidence of inflammatory arthritis, along with positivity for rheumatoid factor (RF) and anti-CCP (> 500 IU/ml). The patient met the 2010 classification criteria for RA with a score of 8, established by the American College of Rheumatology/European League Against Rheumatology (ACR/EULAR).[7] Until 2022, there was no history of treatment other than oral methotrexate 15 mg per week, which had clinically controlled her disease. Apart from the diagnosis of RA, she had no comorbidities, family history of autoimmune disease or smoking history. In 2022, the patient applied to the rheumatology clinic with complaints of red rashes on the cheeks, sores in the mouth, hair loss, fever and increased joint pain. Physical examination revealed severe malar rash, oral ulcers, and alopecia, with swelling in the bilateral metacarpophalangeal joints and wrists. (Figure 1 and Figure 2). Hand radiographs revealed periarticular osteoporosis and narrowings between the joints (Figure 3) The patient's vitals showed a temperature of 37.8°C. There was no evidence of hypotension or tachycardia. In the application laboratory, Antinuclear antibody was positive at 1/160 dilution and had a homogeneous pattern. Anti-Sm and anti-ds-DNA positivity was detected in the patient's extractable nuclear antigen profile (ENA). The patient had hypocomplementemia in serological profile, with C3 level of 0.75 g/L (normal value: 0.9 - 1.8) and C4 level of 0.11g/L (normal value: 0.1 - 0.4). As a result of the evaluations, the patient was diagnosed with SLE according to the ACR/EULAR 2019 classification criteria with a score of 33.[8] Since she also had seropositive RA, we were following up with the diagnosis of Rhupus syndrome. In other laboratory findings: creatinine: 0.9 mg/dL (normal value: 0.7-1.20 mg/dL), C- reactive protein (CRP): 32 mg/L (normal value: 0-5 mg/dL), erythrocyte sedimentation rate: 61 mm/hour (normal value: 0-20 mm/hour), hemoglobin: 8.3 g/dL (normal value: 12-16 g/dL), platelet count: 112.103/µL (normal value: 150-450.103/µL) were detected. This anemia and thrombocytopenia were thought to be autoimmune. Coombs tests were positive, and the peripheral blood smear revealed no schistocytes, with thrombocytes appearing normal. Transferrin saturation was 30%, ferritin was 29 ng/ml (normal range: 13-150 ng/ml), mean cell volume was 86 femtoliters (normal range: 80-100), folate was 8 ng/ml (normal range: 2.7-17), and vitamin B12 was 300 pg/ml (normal range: 160-950). Considering the clinical condition and laboratory parameters, hydroxychloroquine 200 mg twice

a day and methylprednisolone (24 mg) were added to the patient's treatment. The steroid dose was gradually reduced to 8 mg/day. After a two-month follow-up, significant improvement was observed in the patient's clinical condition, including a reduction in mouth sores, hair loss, and joint symptoms and swellings. In the blood taken during this follow-up, CRP: 16 mg/L, platelet count: 132.103/µL, and hemoglobin: 9.3 g/dL were detected. Going forward, the plan is to further reduce the steroid dose to 5 mg/day based on the clinical situation, introduce mycophenolate mofetil to the treatment in combination with methotrexate.

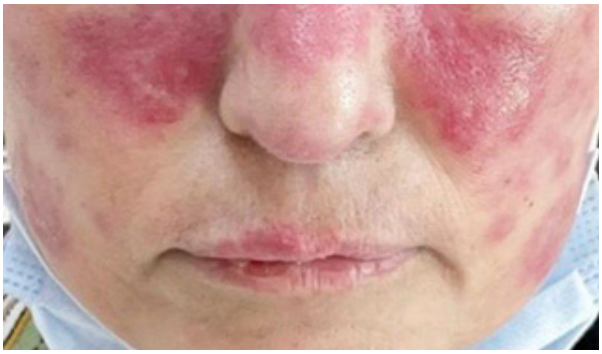

Figure 1: Severe malar rash of our patient

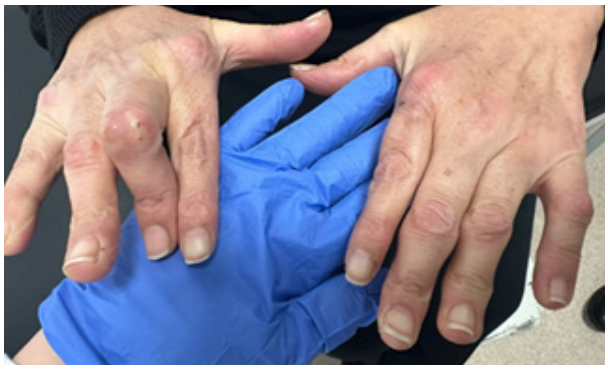

Figure 2: Swelling in metacarpophalangeal joints and wrists, hand deformities

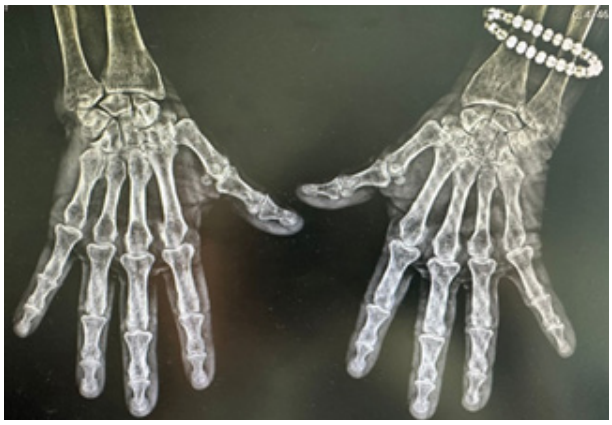

Figure 3: Hand X-ray

Discussion

The diagnosis of Rhupus syndrome can be quite challenging due to the absence of specific classification criteria.[9] Previous case series have suggested that Rhupus should be considered in patients with SLE symptoms who also present with anti-CCP positivity and elevated CRP levels, a condition generally observed in women.[10]

In our case, the diagnosis was supported by the presence of chronic symmetric polyarthritis, malar rash, alopecia, mucosal involvement, and hematological manifestations, all of which developed in the course of SLE. Although skin biopsy is not deemed essential for diagnosis according to the literature, it can be helpful in ruling out other erythematous diseases.[11] However, we opted not to perform a skin biopsy due to the involvement of multiple systems and the simultaneous presence of anti-Smith, anti-CCP, and anti-dsDNA antibodies. While some rheumatologists may categorize RhS as a subtype of SLE, the coexistence of anti-Smith and anti-CCP antibodies alongside ANA and RF positivity in our patient suggests that RhS is more appropriately characterized as an overlap syndrome rather than a distinct type of SLE.[12] Furthermore, the elevated levels of anti-CCP and CRP observed in our patient align with the serological profile typically associated with RhS.

The literature suggests that, in the majority of cases, the diagnosis of RA precedes the diagnosis of SLE by several years, with SLE developing within four to seven years after the initial RA diagnosis.[10] In accordance with this pattern, in our case, RA manifested three years before the diagnosis of SLE. It is noteworthy that renal and neurological involvement is less frequently observed in RhS compared to SLE patients without a prior RA diagnosis. For instance, glomerulonephritis and serositis appear to be rare in comparison to SLE cases.[13] High disease activity in SLE, the use of high steroid doses during induction, or the necessity for pulse steroid therapy are less common in Rhupus patients. Similarly, in our case, we observed improvement in both clinical and laboratory parameters before the need for pulse steroids arose.

Genetic studies are also highlighted in the literature as a diagnostic tool for the disease. It has been recognized that genes such as programmed cell death 1 (PDCD1), signal transducers and activators of transcription 4 (STAT4), and protein tyrosine phosphatase nonreceptor 22 (PTPN22) are associated with RA and SLE. Additionally, some studies indicate that hu-

man leukocyte antigen (HLA) DR1 and DR2 alleles are more prevalent in Rhupus syndrome.[14] However, due to the financial conditions of our country, genetic testing was not conducted on our patient.

Symmetrical and bilateral erosive joint damage was evident in the physical examination and hand radiograph of our patient. The symmetric bilateral erosive arthritis pattern aligns with one of the 2020 EULAR/ACR classification criteria for RA. Additionally, according to research by Chan et al., SLE patients who test positive for anti-CCP are more prone to develop erosive arthritis.[15] There is a belief that anti-CCP may play a pathogenic role in erosions. Consistent with this, erosive arthritis was observed in our patient.

There is limited information available on the treatment of RhS, and the existing data are primarily derived from a small number of case studies and series. Treatment regimens typically involve low-to-moderate doses of corticosteroids combined with multiple disease modifying anti rheumatic drugs (DMARDs, such as methotrexate) in Rhupus patients with significant joint involvement to prevent the progression of erosive arthritis.[16] We also implemented this treatment for our patient. But in some studies have indicated that DMARDs alone may not be adequate for managing RhS.[5] Mycophenolate mofetil and cyclosporine have both proven effective in treating RhS.[10,17] In contrast, anti-TNF therapies have shown minimal benefits for Rhupus or SLE and, despite their success in RA, have been reported to exacerbate RhS in some cases.[9] However, if internal organ involvement develops or if there is clinical deterioration, options such as mycophenolate mofetil, other biological treatments, rituximab, and abatacept may be considered.[18,19] In our case despite concurrent thrombocytopenia and anemia, a positive response to the treatment was achieved without the need for mycophenolate mofetil.

This case outlines the presentation of a 42-year-old woman with erosive arthritis accompanied by mucosal findings, diagnosed and followed as Rhupus syndrome. Our patient showed a positive response to the treatment involving steroids and hydroxychloroquine. To the best of our knowledge, this represents the tenth reported case of adult Rhupus syndrome in our country. Additionally, we aimed to enhance awareness among RA patients regarding the potential co-occurrence of SLE in the course of their condition. Approaching it from this perspective may prove beneficial, particularly for young female RA patients.

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