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RHUPUS: CLINICAL ANALYSIS OF A NEWLY REPORTED CASE

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ABSTRACT

Rhupus syndrome is a rare clinical condition characterized by the coexistence of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), presenting unique diagnostic and therapeutic challenges in the field of rheumatology. This article details the clinical presentation, diagnostic criteria, and management of a newly identified case of Rhupus syndrome with significant renal involvement. We describe the case of a 25-year-old North African woman with a complex medical history, who presented with symptoms indicative of both RA and SLE, including inflammatory polyarthralgia, facial erythema, and nephrotic syndrome. Comprehensive laboratory investigations, imaging studies, and a renal biopsy confirmed the diagnosis. The patient was treated with a combination of corticosteroids, cyclophosphamide, hydroxychloroquine, and azathioprine, leading to significant clinical improvement. This case highlights the importance of recognizing Rhupus syndrome as a distinct overlap syndrome and underscores the need for tailored therapeutic approaches to manage the complexities associated with simultaneous RA and SLE. Continued research is essential to further elucidate the pathogenesis of Rhupus syndrome and optimize treatment strategies for affected patients.

KEYWORDS: Comprehensive laboratory investigations, imaging studies, and a renal biopsy confirmed the diagnosis.

INTRODUCTION

Rhupus syndrome is an uncommon clinical entity defined by the simultaneous presence of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). The first clinical observation of this condition was reported by Toone in 1960, who described cases exhibiting features of both diseases. In 1971, Peter Schur introduced the term "Rhupus" to categorize patients with overlapping clinical and laboratory characteristics of RA and SLE. These systemic autoimmune rheumatic diseases can affect multiple organ systems and exhibit distinct clinical and serological features.

Globally, Rhupus syndrome affects approximately 0.01% to 2% of patients with rheumatic diseases, highlighting its rarity and the complexity of its manifestations. Despite a growing number of case reports, our understanding of Rhupus remains limited. This article aims to contribute to the literature by presenting a comprehensive analysis of a newly identified case of Rhupus syndrome with renal involvement from the Centre of Nephrology at Hospital Ibn Sina, Rabat.

CASE REPORT

We present the case of a 25-year-old North African woman with a complex medical history of sickle cell disease, treated with folic acid since childhood. She was admitted for lower limb edema and inflammatory polyarthralgia. Over the past year, she developed chronic polyarthritis affecting both wrists and ankles, accompanied by recent-onset facial erythema exacerbated by sun exposure.

Upon examination, the patient was tachycardic, normotensive, and afebrile, exhibiting clinical signs of facial erythema, bilateral wrist synovitis, and noticeable hair loss. She presented with soft, pitting edema of the lower limbs. Urinalysis revealed proteinuria. Musculoskeletal examination showed hyperextension deformities in the proximal interphalangeal (PIP) joints

and hyperflexion deformities in the distal interphalangeal (DIP) joints of both hands (Figure 1). X-ray imaging demonstrated periarticular erosions, supporting the clinical findings (Figure 2).

Laboratory investigations revealed normochromic normocytic anemia (Hb: 7 g/dL), neutropenia (PNN: 4000/mm³), normal creatinine levels, nephrotic syndrome with proteinuria (4 g/24h), hypoalbuminemia (albumin: 28 g/L), and elevated inflammatory markers, with an erythrocyte sedimentation rate of 30 mm/hr. She tested positive for rheumatoid factor (65 UI/ml), anti-cyclic citrullinated peptide antibodies (122 UI/ml), and antinuclear antibodies at a titer of 1/640. Her anti-dsDNA antibody was positive, along with low complement levels (C3).

A renal biopsy confirmed secondary membranoproliferative glomerulonephritis associated with lupus. Immunofluorescence revealed granular peritubular staining with IgG, perinuclear interstitial staining with IgG, and C1q showing fine granular segmental staining, further supporting the diagnosis of lupus (Figures 3-5). Based on her clinical presentation, laboratory findings, renal biopsy results, and serology, she met the criteria for both RA and SLE. Specifically, she satisfied four criteria from the American College of Rheumatology (ACR) for RA and four criteria from the Systemic Lupus International Collaborating Clinics (SLICC) for SLE, leading to a diagnosis of Rhupus syndrome.

Treatment included a 500 mg corticosteroid pulse for three days, followed by gradual tapering, combined with monthly cyclophosphamide at 500 mg for six months. Maintenance therapy consisted of hydroxychloroquine 200 mg twice daily and azathioprine 2 mg/kg/day. After six months of treatment, she showed significant improvement, with resolution of proteinuria and preserved renal function. Regarding her rheumatoid arthritis, there was a regression of polyarthralgia, particularly in the hands, and she was scheduled for regular follow-up.

Figures

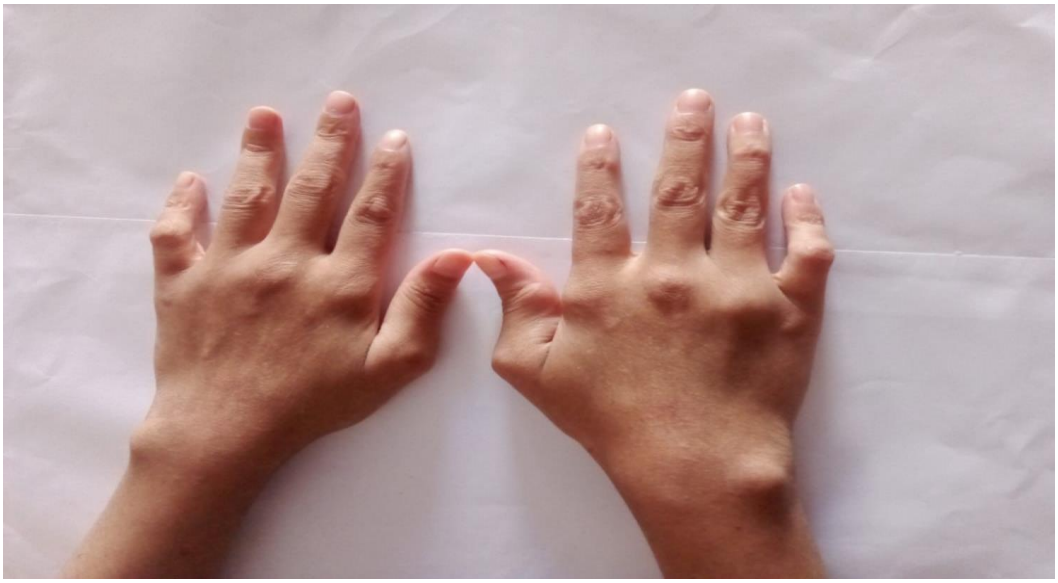

Figure 1: Hand deformities in PIP and DIP joints.

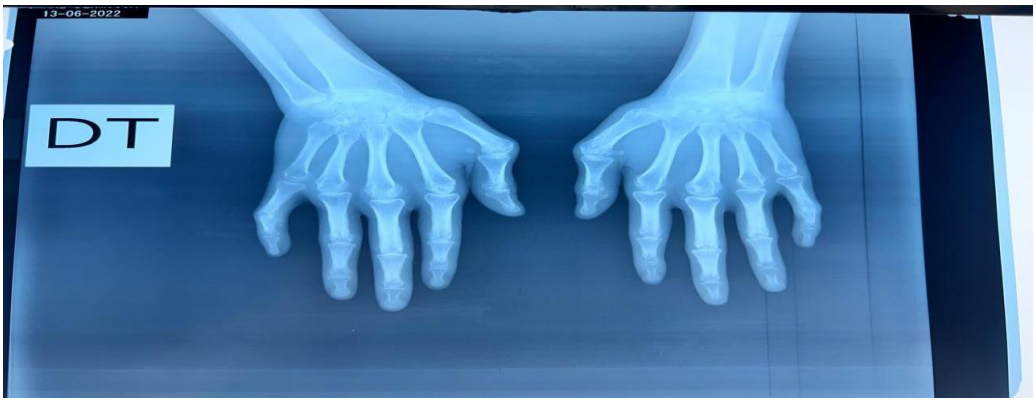

Figure 2: X-ray of hands showing periarticular erosions in proximal interphalangeal and metacarpophalangeal joints.

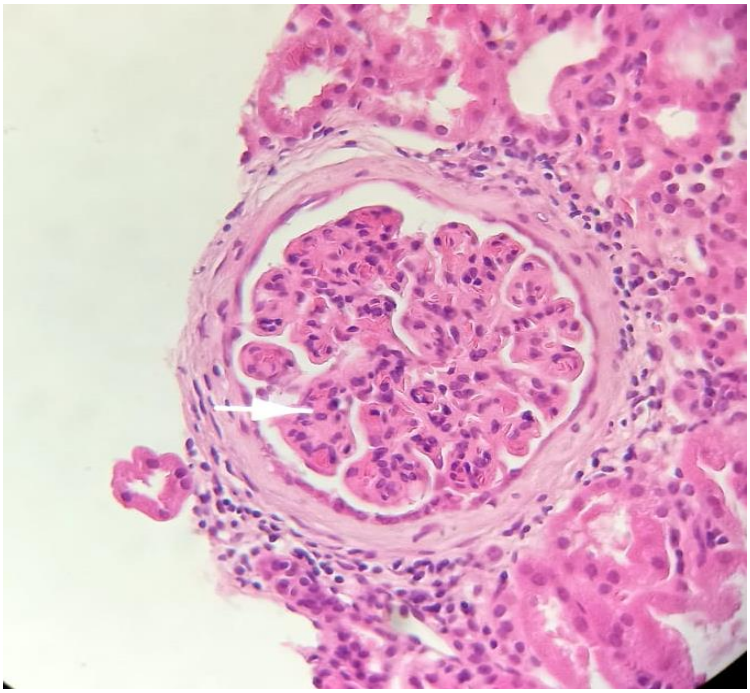

Figure 3: Light microscopy ×40 (Hematoxylin and Eosin): A membranoproliferative glomerulus.

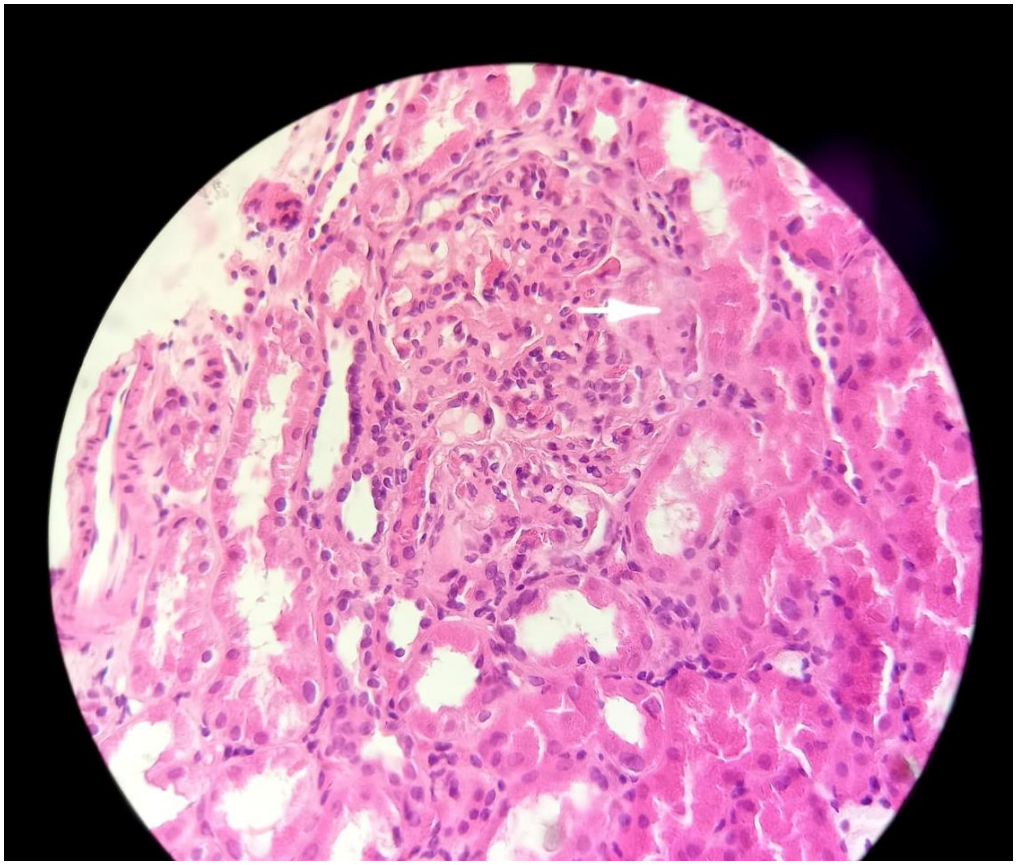

Figure 4: Renal biopsy showing a focus of karyorrhexis.

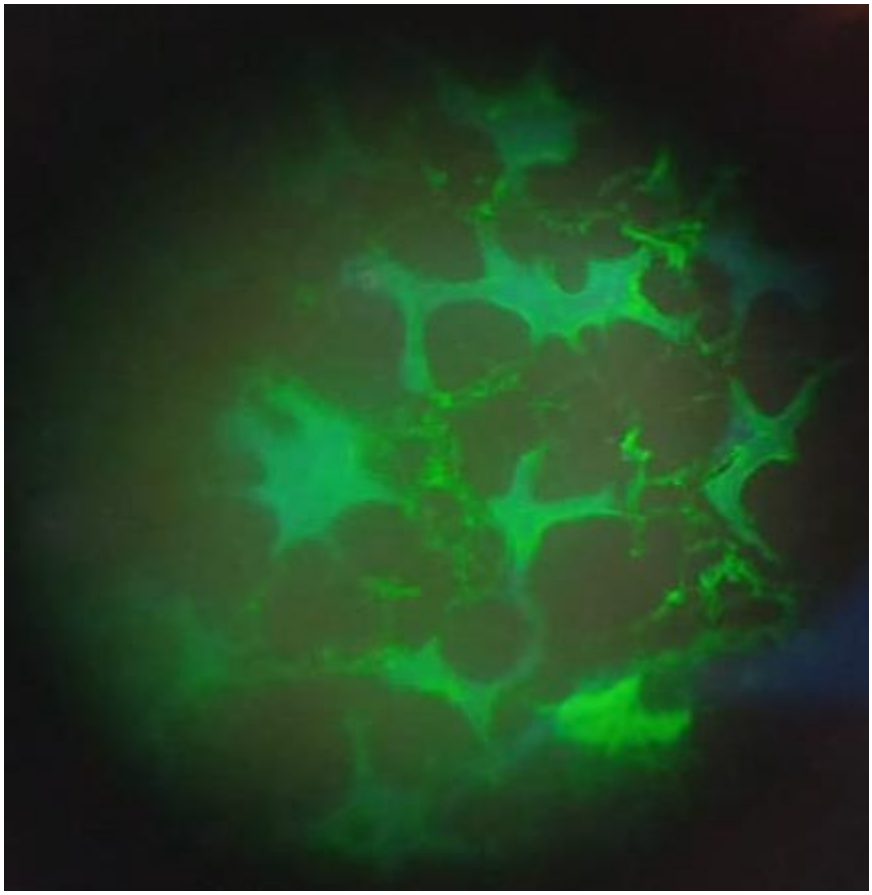

Figure 5: Granular peritubular staining with IgG observed in renal biopsy immunofluorescence.

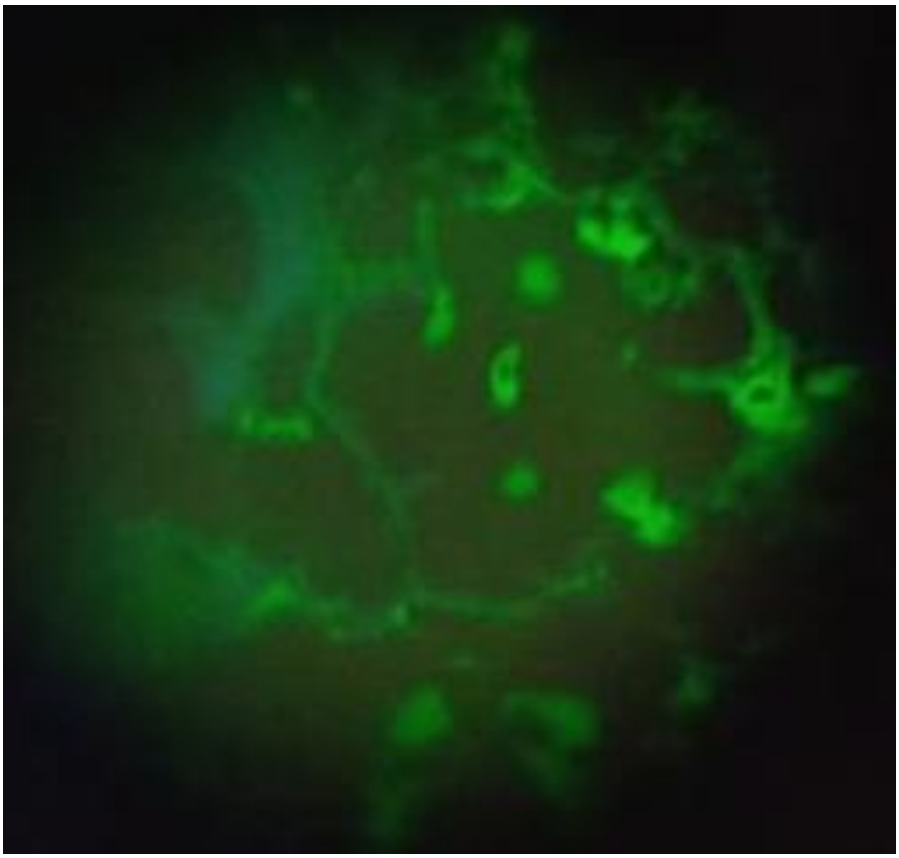

Figure 6: Perinuclear interstitial staining with IgG observed in renal biopsy immunofluorescence.

DISCUSSION

Rhupus syndrome presents a diagnostic challenge due to the absence of distinct criteria. It predominantly affects females and typically presents with RA-like symptoms before SLE features emerge. In rare instances, both conditions manifest simultaneously; however, SLE symptoms often appear four to seven years after the onset of RA. In our case, bilateral erosive polyarthritis preceded SLE manifestations by eight months.

Common clinical manifestations of Rhupus syndrome include erosive polyarthritis, rheumatoid nodules, malar rash, photosensitivity, alopecia, and constitutional symptoms, while renal and neurological involvement are less frequent. Our patient initially presented with erosive polyarthritis similar to RA symptoms, followed by the emergence of SLE symptoms, including nephrotic syndrome, cytopenia, polyserositis, and non-scarring alopecia. Notably, she did not develop severe complications such as neurological involvement or rheumatoid nodules. Joint manifestations in SLE vary and include arthralgias and non-erosive polyarthritis with reversible deformities, such as swan neck deformities and ulnar deviation.

Diagnostic evaluations play a pivotal role in confirming Rhupus syndrome, with genetic studies implicating RA and SLE-associated genes, including programmed cell death 1 (PDCD1), signal transducers and activators of transcription 4 (STAT4), Fc-receptor-like 3 gene (FCRL3), and protein tyrosine phosphatase non-receptor 22 (PTPN22). The higher prevalence of human leukocyte antigen (HLA)-DR1 and HLA-DR2 alleles in Rhupus patients underscores genetic predisposition, although financial constraints precluded genetic testing in our case.

Anti-CCP antibodies serve as valuable discriminators between RA and Rhupus versus SLE. In our case, the detection of anti-dsDNA and anti-CCP antibodies confirmed overlapping RA and SLE in Rhupus syndrome, rather than representing a distinct subtype of SLE. Imaging studies revealed symmetric bilateral erosive polyarthritis, consistent with ACR criteria for RA diagnosis. Chan et al. suggest that anti-CCP antibody-positive SLE patients are predisposed to erosive arthritis. The diagnostic criteria for Rhupus, according to some authors, include the presence of erosive symmetrical polyarthritis, clinical manifestations of SLE, and the presence of anti-DNA or anti-Sm antibodies.

Therapeutic strategies for Rhupus syndrome include hydroxychloroquine, corticosteroids, and methotrexate for joint inflammation and constitutional symptoms, with mycophenolate mofetil and biologics considered for renal involvement. We treated our patient with a bolus of corticosteroids (500 mg for three consecutive days), followed by oral corticosteroids at a dose of 1 mg/kg/day and monthly cyclophosphamide infusions (six sessions) as acute treatment. For maintenance, we administered azathioprine at a dose of 2 mg/kg/day, resulting in favorable clinical and biological outcomes.

Biologics, including TNF-alpha inhibitors, require vigilant monitoring due to their potential to exacerbate or induce SLE symptoms when methotrexate monotherapy fails to effectively control erosive RA. Continuous clinical assessment is crucial to preempt potential complications in managing this complex overlap syndrome.

CONCLUSION

Rhupus syndrome, characterized by the coexistence of RA and SLE, presents a unique diagnostic and therapeutic challenge due to its rarity and overlapping clinical features. Clinicians must maintain a high index of suspicion for Rhupus when encountering patients with atypical joint manifestations and systemic autoimmune symptoms. Diagnostic precision, incorporating serological markers and imaging studies, is crucial for timely intervention and effective management strategies tailored to individual patient needs. Continued research is essential to further elucidate the pathogenesis and optimize therapeutic outcomes in this complex overlap syndrome.

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