"Diagnostic Dilemma of Rhupus or Undifferentiated Connective Tissue Disease Complicated by Psoriasis: A Case Report"

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Key Clinical Message:

We report a rare case of psoriasis which developed "Rhupus" overlap disease. Diagnosing multiple connective tissue disease is challenging as most of them mimics similar symptoms. The diagnostic dilemma & treatment strategy we faced will provide guidance towards such patient dealings. Further routine follow up is needed for good prognosis.**Keywords** : Rhupus syndrome, Rheumatoid arthritis, Systemic lupus erythematosus (SLE), Psoriatic arthritis (PsA), Autoimmune overlap syndrome, Case report

Introduction:

Rhupus syndrome is an uncommon but significant clinical condition, with an estimated prevalence rate of just 0.09% [1]. Recognizing and understanding this disorder is crucial for effective diagnosis and treatment. "Rhupus," or "Rhupus syndrome," is a rare and overlooked condition that deserves greater attention. It is characterized by symptoms associated with systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) in the same individual[2]. Despite its complexity, rhesus remains poorly understood, highlighting the necessity for further research and awareness in the medical community. It is a rare, neglected, incompletely understood, and thus debated condition that is commonly considered to feature the presence of symptoms of both SLE and rheumatoid arthritis (RA) in the same patient. Furthermore, psoriasis in the same patient creates a more challenging issue. It may be due to the similarity in genetic pathways between SLE & and Psoriasis, which may have made this co-existence[3]. Evidence also presents that paradoxically treating psoriatic patients with DMARD may result in new autoimmune diseases[4]. We recently encountered an intriguing case involving a 24-year-old man who presented with a long-standing history of polyarthritis and distinct hyperpigmented skin lesions. Initially diagnosed with psoriatic arthropathy, further investigation unveiled a fascinating complexity of autoimmune conditions, hinting at the potential of rhupus or undifferentiated connective tissue disease (UCTD). Despite ongoing treatment for psoriasis, the patient wasn't responding as expected, calling for deeper diagnostic exploration. After careful consideration and consultations among expert clinicians, it became evident that we were facing an overlap syndrome. While navigating the diagnostic maze between undifferentiated connective tissue disease and rhupus, the team came to a unanimous

and hopeful conclusion: this is indeed rhupus. This report highlights the intricate diagnostic journey, the therapeutic strategies we explored, and the clinical challenges we faced while managing this unique patient.

Case History/ Examination:

A 24-year-old normotensive, non-diabetic, non-asthmatic male from Chandpur was admitted to a tertiary medical hospital in Dhaka in May 2024 with a ten-month history of gradually worsening multiple joint pain. The pain began in the small joints of the hands and feet and later involved the shoulders. He also presented with hyperpigmented patches of varying sizes and shapes over the scalp, extensor surfaces of the elbows, dorsum of the hands, back, extensor thighs, knees, and feet. These lesions were initially erythematous and scaly without oozing, discharge, or bleeding upon scratching. Scalp hair loss and unintentional weight loss of 25 kg were also noted over the past eight months, accompanied by a reduced appetite, but no gastrointestinal or cardiopulmonary symptoms. Low-grade, intermittent fever (maximum 101°F) had persisted for six months, along with generalized weakness over four months, leading to difficulties in squatting, sitting up, and climbing stairs, requiring assistance for daily activities. Six months prior to this admission, the patient had been treated for "Psoriasis with Psoriatic arthropathy" with methotrexate, sulfasalazine, topical calcipotriol, steroids (betamethasone), and urea. However, treatment complications, including methotrexate-induced oral mucositis, necessitated medication changes. Sulfasalazine was discontinued after two weeks due to recurrent mucositis, and "Apremilast" was initiated, although it provided minimal relief for joint pain. The patient denied any history of eye pain, photosensitivity, genital ulcers, chest pain, or breathlessness, as well as any significant systemic or infectious history, including TB contact or recent travel. He had no significant family medical history, substance use, or risky sexual behavior. His immunization, including for COVID-19, was up to date. Upon examination, the patient appeared ill, moderately anemic, and underweight, with a BMI of 14.8 kg/m^2. Skin inspection revealed multiple hyperpigmented patches on the extremities and trunk (Figure 1A-C), without scaling in most areas. There was diffuse scarring alopecia (Figure 1D), particularly over the scalp. Notably, an erythematous patch with silvery-white scales was observed on the back of the trunk (Figure 2). Musculoskeletal examination showed swelling, tenderness (Grade-IV), hyperpigmentation, and raised temperature over the metacarpophalangeal (MCP) and proximal interphalangeal (PIP) joints of both hands (Figure 3), accompanied by dorsal guttering and wasting of the thenar and hypothenar muscles. Shoulder abduction was painful and restricted bilaterally (Figure 4), while hip movements were similarly painful and limited. Neurologic examination was unremarkable, but needle electrode examination (NEE) indicated asymmetric sensory neuropathy, consistent with mono-neuritis multiplex, with early signs of myopathy or neuromyopathy. Methods (Differential diagnosis, investigations and treatment): Upon admission, a comprehensive diagnostic approach was undertaken to address the patient's complex presentation. A skin biopsy conducted nine months prior revealed hyperkeratosis, parakeratosis, Munro's abscess, and dilated capillaries in the dermal papilla, consistent with psoriasis. Further evaluation of the patient's reduced muscle bulk and power led to a muscle biopsy, which showed mild variation in muscle fiber diameter, internalized nuclei, and scant inflammatory infiltration, suggesting muscular dystrophy. Initial laboratory investigations revealed normocytic normochromic anemia (hemoglobin: 9.3 g/dL), leukopenia (WBC: 3640/mm^3), thrombocytopenia (90,000/mm^3), elevated ESR (46 mm/h), and creatine phosphokinase (307 U/L). Notably, ANA was moderately positive, and anti-CCP levels were low positive (17.98 U/mL), along with severe vitamin D deficiency (9.1 nmol/L). Imaging studies of the chest, spine, and pelvis showed mild osteopenia, with normal ECG and echocardiography findings. Given the overlapping clinical features, differential diagnoses included rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), dermatomyositis, and mixed connective tissue disease (MCTD). However, the negative ENA (Extractable nuclear antigen) profile and muscle biopsy findings excluded dermatomyositis and MCTD. Based on the American College of Rheumatology (ACR) criteria, with 9 out of 10 points, the patient was diagnosed with RA, supported by joint involvement, elevated ESR, low-positive Anti-CCP, and symptoms persisting for more than six weeks. Additionally, the presence of positive ANA, pancytopenia, non-scarring alopecia, and synovitis aligned with SLE. Psoriasis, confirmed via skin biopsy 9months ago, further complicated the case. Ultimately, a diagnosis of "Rhupus" overlap syndrome

was made and undifferentiated connective tissue was kept as alternative differential. The patient was treated with prednisolone 20mg (0.5mg/Kg) and hydroxychloroquine 200mg (5mg/Kg), targeting RA and SLE. Psoriasis was managed with topical therapies, and muscular dystrophy was addressed through supportive care, including physical therapy. Vitamin D(40,000IU) supplementation was initiated to correct the deficiency. Conclusion and Results (Outcome and follow-up): In conclusion, diagnosing "Rhupus" overlap syndrome is inherently challenging, requiring thorough exploration and exclusion of other autoimmune conditions when patients present with non-specific symptoms beyond their primary disease. Our patient, initially diagnosed with psoriasis, benefited from this comprehensive approach, which allowed for a more holistic treatment strategy. This resulted in both patient satisfaction and a favorable prognosis. During a follow-up two months later, the patient showed marked improvement, including better shoulder abduction (Figure 5), weight gain (BMI: 16.3 kg/m^2), and a reduction in joint line tenderness from grade 4 to grade 1.

Discussion:

Psoriasis is a chronic autoimmune skin condition that leads to rapid skin cell production, resulting in scaling and inflammation, and is often linked with other autoimmune diseases, including RA and SLE[5]. In patients with rhupus, psoriasis can exacerbate the complexity of treatment, as both RA and SLE may influence the severity and presentation of skin lesions. Moreover, psoriasis can also lead to psoriatic arthritis (PsA), an inflammatory arthritis affecting some individuals with psoriasis, further complicating the clinical picture[6]. Managing rhupus with psoriasis requires a careful and tailored approach, considering the overlapping symptoms and potential for multi-organ involvement, as seen in patients with systemic vasculitis[7]. The pathophysiology of Rhupus syndrome involves immune-mediated mechanisms characteristic of both RA and SLE, including the production of autoantibodies and systemic inflammation. Anti-cyclic citrullinated peptide (Anti-CCP) and rheumatoid factor (RF) are biomarkers commonly used in diagnosing RA. At the same time, antinuclear antibodies (ANA) and anti-double stranded DNA (anti-dsDNA) are hallmark features of SLE. However, in Rhupus, these markers often overlap, making it difficult to distinguish between RA and SLE early in the disease process[8]. This case was initially underscored due to psoriasis, which neglected the need to evaluate other causes of arthritis further. But eventually, thorough examination & lab workup lead to the correct etiology of arthritis. Since DMARD "Apremilast" didn't show any response, it came to our suspicion that something else pathophysiology must work in this patient. Overlapping features of rheumatoid arthritis and SLE and some non-specific systematic findings made this case more complex. Rhupus is a rare disease with no established criteria or guidelines to treat. We want to notify this case to warrant more attention from policymakers and clinicians to get insights to implement this future research. Our current literature notifies that treatment typically involves a combination of medications and lifestyle changes to manage symptoms and improve quality of life. However, the exact etiology and triggers of rhupus remain unknown, with genetic, immunological, hormonal, and environmental factors potentially playing a role[9,10]. Author Contribution:**Asif Amin:** Conceptualization, Data curation, Writing – review and editing**Zahin Shahriar:** Methodology, Formal analysis, Writing – original draft**Minhajul Hossain:** Project administration, Supervision**Rahatul Ishakh:** Investigation, Software**Shah Tanvir:** Validation, Resources, Visualization

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Ethical Approval

Institutional review board approval did not apply to this case.

Consent

Written informed consent form was obtained from the patient to publish this report in accordance with the journal's consent policy.

Declaration of AI use

For improving readability Grammarly and for paraphrasing Quillbot has been used.

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None. Conflict of interest We declare that we have no conflict of interest. Data availability statement Data will be available on reasonable request from the corresponding author.

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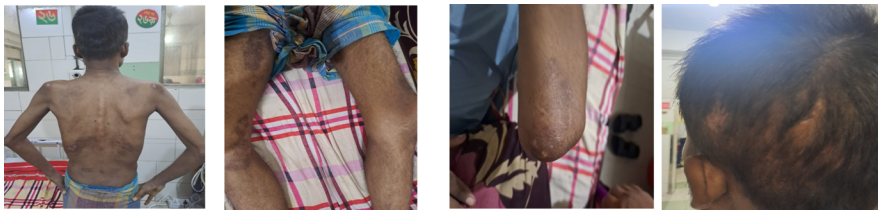

Figure 1: (A-C) shows multiple hyperpigmented patches, and (D) shows diffuse scarring alopecia.

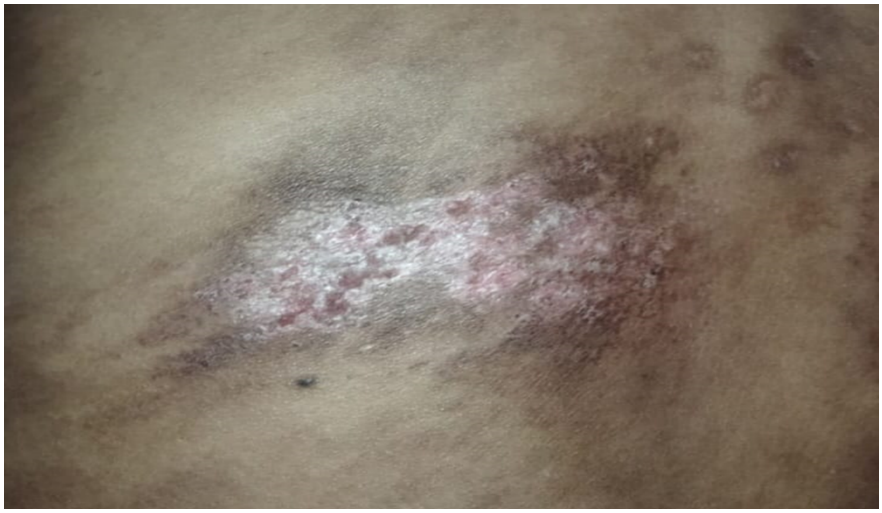

Figure 2: Erythematous patch with the silvery-white scale on the back of the trunk.

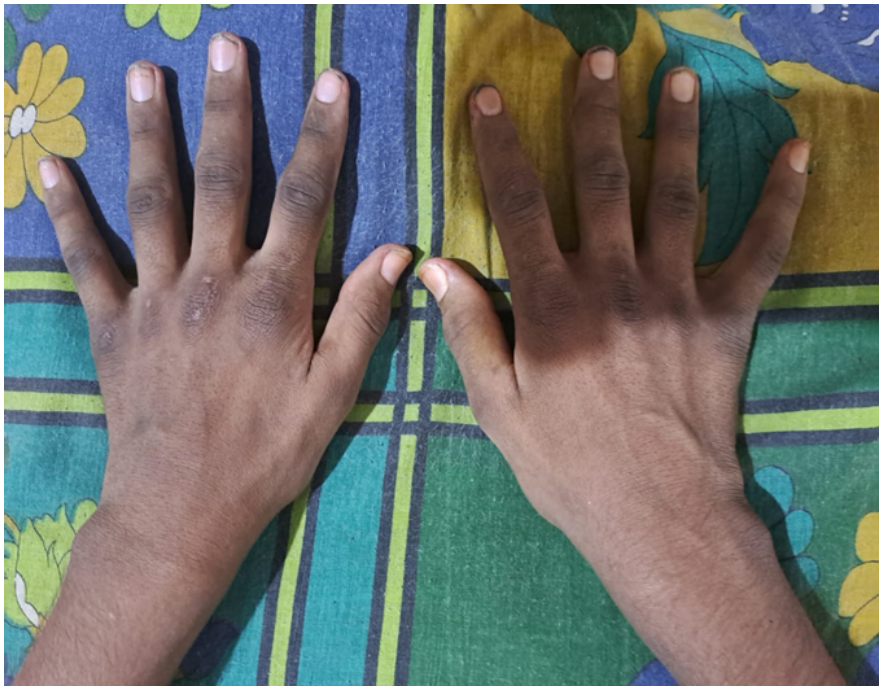

Figure 3: Swollen metacarpophalangeal and inter-phalangeal joints with hyperpigmentation

Figure 4: Shoulder abduction restricted on both sides

Figure 5: Patient able to abduct >45˚after receiving treatment.