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RHUPUS SYNDROME REVEALED BY LIFE-THREATENING AUTOIMMUNE CYTOPENIAS AND ASSOCIATED WITH A RENAL NON-LANGERHANS CELL HISTIOCYTIC GRANULOMATOUS INFILTRATE: A CASE REPORT AND UPDATED LITERATURE REVIEW

Soukaina Mounsif*[1], Mina Moudatir[2], Khadija Echchilali[2], Meriem Benzakour[2], Hassan El Kabli[2]

[1]Resident, Department of Internal Medicine, Ibn Rochd University Hospital, Casablanca, Morocco.

[2]Professor, Department of Internal Medicine, Ibn Rochd University Hospital, Casablanca, Morocco.

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***Corresponding Author: Soukaina Mounsif**
Resident, Department of Internal Medicine, Ibn Rochd University Hospital, Casablanca, Morocco.
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ABSTRACT

Background: Rhupus syndrome is a rare overlap condition combining features of rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE). While hematologic abnormalities are frequent in SLE, severe bleeding secondary to profound immune thrombocytopenia (ITP) as a presenting manifestation of rhupus is exceptional. Concomitant histiocytic disorders are rarely described. **Case presentation:** A 42-year-old Moroccan woman was admitted for severe hemorrhagic syndrome (Khellaf bleeding score 20) with active inflammatory polyarthritis. She had pallor, lower-limb purpura, malar rash, and fusiform finger swelling with positive squeeze test. Labs showed aregenerative normocytic anemia (Hb 6 g/dL), profound thrombocytopenia (<10,000/mm³), and positive direct Coombs test; bone marrow was normal and viral serologies were negative. Immunology revealed ANA 1:640, anti-dsDNA positivity, rheumatoid factor 60 U/mL, anti-CCP 50 U/mL, and CRP 30 mg/L. Ultrasound confirmed active polyarthritis of wrists and hands. Rhupus syndrome was diagnosed (2010 ACR/EULAR RA score 7; 2019 ACR/EULAR SLE score 16). Extension work-up showed normal renal function and negative proteinuria but low complement and anti-dsDNA persistence, consistent with moderate SLE activity. CT scan revealed a pelvic renal mass-like lesion; biopsy demonstrated a CD68-positive granulomatous histiocytic infiltrate consistent with non-Langerhans cell histiocytosis. She received IV methylprednisolone pulses followed by oral prednisone, plus azathioprine and hydroxychloroquine, with rapid clinical and biological improvement and marked radiological regression of the renal lesion. **Conclusion:** This case highlights a rare rhupus presentation dominated by life-threatening autoimmune cytopenias and an unusual renal histiocytic granulomatous infiltrate responding to immunosuppression. It underscores the need for early recognition, careful differential diagnosis, and multidisciplinary management.

KEYWORDS: rhupus; systemic lupus erythematosus; rheumatoid arthritis; immune thrombocytopenia; autoimmune hemolytic anemia; non-Langerhans histiocytosis; renal pseudotumor.

INTRODUCTION

Rhupus syndrome refers to the coexistence in the same patient of clinical, serological, and sometimes radiographic features of both RA and SLE. Initially described by Panush and colleagues, rhupus has since been characterized as a rare but clinically meaningful overlap, most often occurring in women and typically dominated by erosive inflammatory polyarthritis accompanied by lupus-related systemic manifestations and autoantibodies.[1,2] Cohort data and systematic reviews suggest that rhupus frequently evolves with more aggressive joint disease than "classic" non-erosive SLE arthritis, and that anti-CCP antibodies may identify patients at risk for erosive damage.[2–5] Hematologic involvement is common in SLE, but the initial presentation with severe bleeding due to profound thrombocytopenia and concomitant autoimmune hemolysis remains uncommon and represents a management emergency.[6–8] Furthermore, histiocytic disorders—particularly non-Langerhans entities—are rare, heterogeneous conditions increasingly viewed through an immuno-inflammatory lens, with consensus documents emphasizing the need for careful clinicopathological classification and evaluation.[9–12] The association between rhupus and histiocytic infiltrative disease is exceptional, raising questions about shared inflammatory pathways.

We report a case of rhupus syndrome revealed by life-threatening autoimmune cytopenias and associated with a renal mass-like CD68-positive granulomatous histiocytic infiltrate, with a detailed literature review and discussion of diagnostic and therapeutic implications.

CASE PRESENTATION

A 42-year-old Moroccan woman with no notable medical history was admitted for a severe hemorrhagic syndrome with polyarticular inflammatory pain and swelling. Bleeding severity was high, with a **Khellaf bleeding score of 20**. Physical examination revealed marked cutaneo-mucosal pallor, purpura of the lower limbs, malar rash, and fusiform swelling of the fingers with a positive squeeze test. No clinical evidence of lymphadenopathy or hepatosplenomegaly was found.

Laboratory evaluation showed severe normocytic normochromic aregenerative anemia (Hb 6 g/dL), profound thrombocytopenia (<10,000/mm³), and a positive direct Coombs test. Bone marrow aspiration was normal. Viral serologies were negative.

Immunological tests demonstrated ANA 1:640, positive anti-dsDNA antibodies, rheumatoid factor 60 U/mL, anti-CCP antibodies 50 U/mL, and CRP 30 mg/L. Musculoskeletal ultrasound showed active synovitis consistent with polyarthritis of wrists and hands.

The diagnosis of rhupus syndrome was retained with fulfillment of **2010 ACR/EULAR RA criteria (score 7)** and **2019 ACR/EULAR SLE criteria (score 16)**. Extension work-up showed normal renal function and bland urine sediment with negative 24-hour proteinuria. Complement levels were low with persistent anti-dsDNA positivity, suggesting moderate SLE activity.

Thoraco-abdomino-pelvic CT scan did not show interstitial lung disease but identified a renal pelvic mass-like tissue process. Biopsy demonstrated a granulomatous histiocytic infiltrate with CD68 positivity, supporting **non-Langerhans cell histiocytosis**.

Because of the life-threatening hemorrhagic syndrome, intravenous methylprednisolone pulses (1 g/day for 3 days) were administered, followed by oral prednisone. Azathioprine (150 mg/day) and hydroxychloroquine (400 mg/day) were initiated as steroid-sparing and disease-modifying therapy.

The patient improved rapidly with regression of bleeding and arthritis, progressive normalization of blood counts, and significant radiological regression of the renal lesion on follow-up imaging.

DISCUSSION

1) Rhupus syndrome: definition and position within the RA–SLE spectrum

Rhupus syndrome is most often conceptualized as a rare overlap condition rather than a simple coincidence of RA and SLE. Since the original description,[1] subsequent reports, cohorts, and systematic reviews have highlighted a recurring profile: (i) erosive, RA-like arthritis, (ii) lupus-associated clinical manifestations (cutaneous, hematologic, renal, serosal), and (iii) combined autoantibody signatures including ANA/anti-dsDNA and RF/anti-CCP.[2–5] In the largest single-center cohort study from China (51 patients), rhupus represented a small proportion of SLE patients and displayed mixed RA/SLE characteristics, supporting its recognition as a clinically relevant overlap.[3]

A key diagnostic challenge is differentiating rhupus from non-erosive lupus arthritis (including Jaccoud-type deforming arthropathy) and from RA with secondary ANA positivity. Anti-CCP antibodies are particularly informative, as they are strongly associated with erosive disease in RA and may help identify erosive “RA-like” joint involvement in patients with lupus features.[4,5,13] Our patient had active inflammatory polyarthritis confirmed by ultrasound and clear dual-seropositivity (anti-dsDNA and anti-CCP), supporting rhupus rather than isolated SLE arthritis.

2) Immunopathogenesis: why erosions and systemic autoimmunity can coexist

The immunobiology of rhupus likely combines mechanisms dominant in each disease: loss of tolerance with autoantibody production (SLE-like) and synovial-driven inflammatory cascades leading to erosions (RA-like). Systemic autoimmunity and organ damage in SLE involve complex interactions between innate and adaptive immunity, immune complexes, complement activation, and cytokine amplification.[14] RA pathogenesis similarly involves cytokine networks and cellular infiltration in synovium with progressive cartilage and bone destruction (15). In rhupus, the concurrence of anti-dsDNA and anti-CCP may reflect parallel autoreactive B-cell responses. Anti-CCP positivity in rhupus has been specifically studied and reinforces the concept that rhupus patients can carry RA-specific autoimmunity rather than nonspecific RF positivity.[4] Clinically, this may translate into a higher risk of joint damage than in SLE alone, influencing therapeutic decisions toward early disease-modifying treatment.

3) Hematologic presentation: life-threatening autoimmune cytopenias in an overlap disease

Hematologic involvement is frequent in SLE, but the spectrum ranges from mild laboratory abnormalities to severe immune-mediated cytopenias with bleeding or hemolysis requiring urgent treatment.[6,7] The management of peripheral blood cytopenias in SLE requires careful exclusion of alternative causes such as infection, drug toxicity, bone marrow failure, and thrombotic microangiopathy, and may involve bone marrow assessment in selected cases.[6] In our patient, a normal myelogram and negative viral serologies supported immune peripheral destruction rather than central suppression.

Severity assessment matters. Platelet count alone correlates imperfectly with bleeding risk. The Khellaf bleeding score was developed to guide management based on clinical bleeding rather than platelet number, and a strategy relying on this score was found relevant and safe in severe autoimmune thrombocytopenic purpura.[7] Our patient's Khellaf score of 20 indicated a high hemorrhagic risk, justifying immediate high-dose corticosteroids.

Treatment principles: Glucocorticoids remain first-line for severe immune thrombocytopenia and autoimmune hemolytic anemia in SLE contexts.[6,8] Intravenous immunoglobulins, rituximab, and thrombopoietin receptor agonists are frequently considered in refractory or relapsing cases, though robust randomized data specifically in SLE-associated ITP are limited and practice relies on case series and expert consensus.[8] A recent concise review emphasizes that thrombocytopenia may be an initial SLE manifestation and requires individualized immunosuppressive strategies.[8]

Importantly, the **EULAR 2023 update** (published 2024) provides contemporary guidance on managing hematologic SLE manifestations and reinforces hydroxychloroquine as a foundational therapy in SLE whenever possible, with add-on immunosuppression tailored to organ involvement and severity.[16]

4) Why hydroxychloroquine + azathioprine was a rational choice here

Hydroxychloroquine is associated with reduced flares and improved long-term outcomes in SLE, with an overall favorable benefit–risk profile.[17] EULAR recommendations continue to place antimalarials as core therapy in most SLE patients, with dose and monitoring adapted to safety considerations.[16]

Azathioprine is widely used as a steroid-sparing agent in SLE, particularly for maintenance therapy or moderate systemic involvement, and is frequently cited among conventional immunosuppressants used in hematologic SLE manifestations.[6,16] In our case, azathioprine was selected to consolidate remission after emergency steroid therapy while hydroxychloroquine addressed the SLE component and contributed to long-term disease control.

5) The unusual renal lesion: CD68-positive granulomatous histiocytic infiltrate and its differential diagnosis

The renal "mass-like" lesion was a pivotal diagnostic issue. In rhupus/SLE, renal involvement typically raises concern for lupus nephritis; however, our patient had normal renal function, bland urinary sediment, and negative proteinuria, making lupus nephritis less likely at that stage. Imaging showing a tissue-density renal pelvic process broadened the differential diagnosis to include malignancy, infection (including tuberculosis), sarcoidosis, inflammatory pseudotumor, IgG4-related disease, and histiocytic disorders.

Histiocytic disorders are heterogeneous. The Mayo Clinic Histiocytosis Working Group consensus statement emphasizes systematic clinicopathologic evaluation and the importance of immunophenotyping (including macrophage markers such as CD68) to classify histiocytoses and guide management.[9] Erdheim–Chester disease (ECD), a prototypical non-Langerhans histiocytosis, is characterized by CD68+ CD1a− histiocytes and may involve retroperitoneal and renal/perirenal tissues, sometimes mimicking mass lesions; consensus guidelines and reviews underscore that tissue diagnosis is essential and that treatment depends on extent and molecular findings.[10–12]

While our case was labeled as non-Langerhans histiocytosis based on histology and CD68 positivity, the broader lesson is that **renal pseudotumoral infiltrates can be inflammatory/histiocytic and steroid-responsive**, and biopsy is crucial to avoid inappropriate surgical or oncologic pathways.

6) Potential links between systemic autoimmunity and histiocytic inflammation (hypothesis)

Although causal association cannot be concluded from a single case, the coexistence of rhupus and a renal histiocytic granulomatous infiltrate suggests overlapping immune activation pathways. SLE is characterized by chronic immune complex–driven inflammation, complement activation, and macrophage engagement.[14] Histiocytic disorders similarly involve macrophage lineage cells with inflammatory activation and, in many cases, MAPK pathway alterations; modern frameworks recognize both inflammatory and neoplastic dimensions depending on the entity.[9–12]

A plausible hypothesis is that a profoundly activated innate immune environment could favor tissue macrophage accumulation and granulomatous histiocytic responses in susceptible individuals. Clinically, the favorable response of the renal lesion to immunosuppression supports an immune-mediated component.

7) Practical implications for clinicians

This case yields several practical messages:

1. **Consider rhupus in patients with erosive-pattern inflammatory arthritis plus lupus serologies**, especially with anti-CCP positivity.[2–5]
2. **Do not underestimate hematologic severity**: use bleeding assessment tools and treat the patient, not the platelet count alone.[7]
3. **Perform a broad etiologic work-up for cytopenias**, excluding infection, drugs, and marrow disease.[6]
4. **Biopsy atypical renal mass-like lesions** in autoimmune patients; not all renal lesions are lupus nephritis or malignancy.[9–12]
5. **Use guideline-supported baseline therapy** (hydroxychloroquine whenever possible) and tailor immunosuppression to severity and organ involvement.[16,17]

8) LIMITATIONS

This is a single case report, and the precise subtype of non-Langerhans histiocytosis and its molecular profile (e.g., MAPK pathway mutations) were not detailed. Future evaluation in similar cases could include extended immunohistochemistry and molecular testing where available, and functional imaging when systemic histiocytosis is suspected.

CONCLUSION

We report a rare case of rhupus syndrome revealed by life-threatening autoimmune cytopenias and associated with a renal CD68-positive granulomatous histiocytic infiltrate with marked response to immunosuppression. This observation expands the clinical spectrum of rhupus and highlights the need for early recognition, rigorous etiologic assessment of cytopenias, histologic confirmation of atypical organ lesions, and multidisciplinary, guideline-informed management.

Declarations

Ethics approval and consent to participate: Written informed consent was obtained from the patient.

Consent for publication: Obtained.

Conflicts of interest: None declared.

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Data availability: Available from the corresponding author upon reasonable request.

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