RESEARCH PAPER

Where Lupus Meets Rheumatoid Arthritis: A Young Woman with Rhupus Syndrome

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ABSTRACT

Background: Rhupus is a rare overlap phenotype characterised by SLE features and serology alongside RA-like erosive inflammatory arthritis. Heterogeneous definitions across decades and the absence of validated rhupus-specific criteria complicate recognition and standardisation of treatment

Keywords: Rhupus syndrome,Systemic lupus erythematosus, Rheumatoid arthritis Overlap syndrome,Anti-CCP antibodies,Erosive arthritis.

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INTRODUCTION

Case presentation

History

A 25-year-old previously healthy woman presented with **1 month of intermittent fever** (typically 38–39°C) and **severe fatigue** limiting routine activity. She had received two outpatient antibiotic courses without sustained benefit , prompting referral for FUO evaluation.

Within 2 weeks of fever onset, she developed **symmetrical inflammatory joint pain** with episodic swelling involving both wrists and multiple MCP and PIP joints. She reported **morning stiffness ~90 minutes** and difficulty making a fist. Systemic review identified **photosensitivity**, **malar facial rash**, and **recurrent painless oral ulcers** . There was no cough, dysuria, diarrhoea, focal infection symptoms, or night sweats . She denied sicca symptoms, psoriasis, inflammatory back pain, genital ulcers, or uveitis . There was no prior thrombosis or pregnancy morbidity .

Medication history excluded common drug-induced lupus triggers (e.g., hydralazine/procainamide) . Family history was noncontributory . She was not pregnant and used reliable contraception , discussed explicitly due to anticipated teratogenic DMARD exposure. Reproductive counselling is recommended “early and often” in rheumatic disease care.

Examination

On presentation, she appeared fatigued but oriented. Vital signs were: temperature 38.4°C, pulse 98/min, BP 108/68 mmHg, RR 16/min, SpO_2 98% room air .

Key findings: - Mild pallor . Malar erythema sparing nasolabial folds . -Shallow oral ulcers on hard palate. Musculoskeletal: active synovitis and tenderness of both wrists; synovitis in MCP 2–5 and PIP 2–5 bilaterally; reduced grip strength . No rheumatoid nodules, vasculitic rash, serositis signs, focal neurological deficits, or frank organ-threatening lupus features on examination .Diagnostic reasoning and criteria

Differential diagnosis and reasoning

Given fever-first presentation with subsequent inflammatory polyarthritis, the differential diagnosis remained broad until objective autoimmune signatures emerged.

Major categories and key reasoning :

Endemic/occult infections (malaria, dengue, enteric fever, TB, endocarditis): fever with elevated inflammatory markers mandates exclusion before immunosuppression escalation. Infection screening and prophylaxis strategies before immunomodulators are formalised in modern EULAR infection guidance for autoimmune inflammatory rheumatic diseases.

Autoimmune inflammatory disease: evolving symmetric small-joint synovitis, mucocutaneous features, and cytopenias strongly support SLE-spectrum disease; erosions and anti-CCP/ACPA support RA-like destructive synovitis.

Adult-onset Still’s disease: fever with arthritis can mimic, but ANA/anti-dsDNA positivity, hypocomplementemia and anti-CCP high titres are not typical.

Hematologic malignancy: can cause FUO and cytopenias, but the emergence of disease-specific autoantibodies and inflammatory arthritis pattern shifts probability substantially.

SLE classification by SLICC-2012

SLICC-2012 classifies SLE if a patient has **≥4 criteria with at least 1 clinical and 1 immunologic**, or biopsy-proven lupus nephritis with ANA/anti-dsDNA.

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SLICC-2012 criteria satisfied in this case :

Domain	SLICC criterion	Evidence in this case
Clinical	Acute cutaneous lupus	Malar rash/photosensitivity
Clinical	Oral ulcers	Recurrent painless ulcers
Clinical	Synovitis	≥2 joints with objective synovitis and morning stiffness
Clinical	Leukopenia/lymphopenia	Leukopenia on CBC
Immunologic	ANA	High-titre ANA by IIF
Immunologic	Anti-dsDNA	Positive above reference
Immunologic	Low complement	Low C3 and/or C4

This exceeds the minimum SLICC threshold and includes both clinical and immunologic criteria.
SLE classification by ACR-1997
ACR-1997 is met when **≥4 of 11** criteria occur across time.
ACR-1997 criteria satisfied : malar rash; photosensitivity; oral ulcers; arthritis; hematologic disorder (leukopenia ± thrombocytopenia); immunologic disorder (anti-dsDNA); ANA positivity. (≥4 achieved.)
RA classification by 2010 ACR/EULAR (score-based)
The 2010 RA criteria classify "definite RA" when synovitis is present in ≥1 joint, **not better explained by another diagnosis**, with total score **≥6/10** across four domains (A–D).
The scoring categories (abbreviated) are:
A. Joint involvement: 0–5 points
B. Serology (RF/ACPA): 0–3 points
C. Acute-phase reactants: 0–1 point
D. Duration: 0–1 point
RA scoring for this patient

Domain	Patient data	Score rule	Points
A. Joint involvement	>10 joints involved, including ≥1 small joint (wrists, MCPs, PIPs; ± others)	>10 joints with ≥1 small → 5	5
B. Serology	High-positive RF and high-positive ACPA (anti-CCP)	High-positive RF/ACPA → 3	3
C. Acute-phase reactants	ESR/CRP elevated	Abnormal APR → 1	1
D. Duration	4 weeks symptoms	<6 weeks → 0	0
Total		**≥6 needed**	**9/10**

Why "rhupus" rather than SLE with arthritis alone?
Large cohort evidence indicates rhupus patients commonly exhibit **radiological erosions** and **higher prevalence of RF/anti-CCP**, with higher ESR/CRP than SLE controls, while showing comparatively lower SLE disease activity and less renal/neurologic involvement overall. This pattern is materially different from classic lupus arthritis which is typically nonerosive.
Investigations

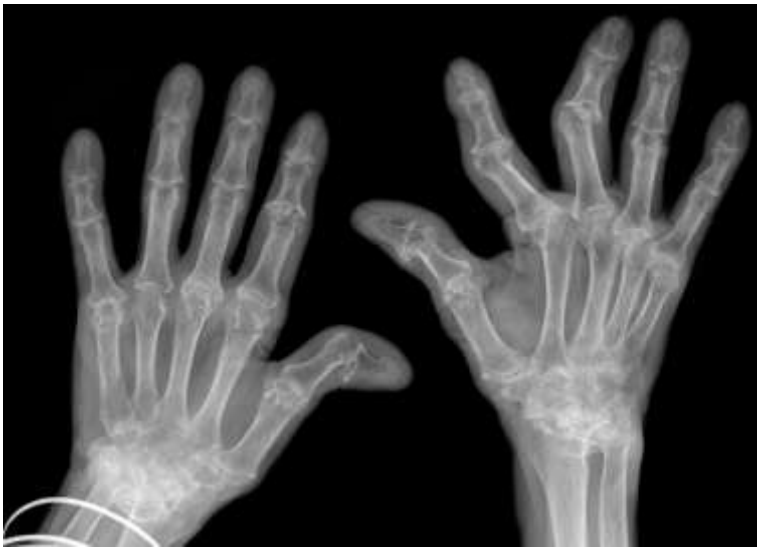
Test domain	Test	Range (typical adult)	Result	Interpretation
Inflammatory markers	ESR	<20 mm/hr	86	Marked inflammation; supports active inflammatory disease
	CRP	<5 mg/L	28	Elevated; in rhupus, CRP may be higher than in typical SLE, but infection must be excluded
Haematology	Haemoglobin	12–15 g/dL	9.6	Anaemia of inflammation ± haemolysis/iron deficiency work-up required
	TLC	4.0–11.0 $\times 10^9$/L	3.1	Leukopenia supports SLE hematologic criterion (SLICC/ACR)
	Platelets	150–400 $\times 10^9$/L	135	Mild thrombocytopenia (supports lupus spectrum; assess trends)

Test domain	Test	Range (typical adult)	Result	Interpretation
Renal	Creatinine	0.6–1.1 mg/dL	0.72	Preserved renal function
	Urine routine	Protein neg; RBC 0–2/hpf	Protein 1+; RBC 10–15/hpf	Suggests glomerular involvement; repeat + quantify
	UPCR	<0.15 g/g	0.62	Sub-nephrotic proteinuria; consider lupus nephritis evaluation
Liver/metabolic	ALT/AST	lab-specific	Mildly elevated	Baseline before MTX; rule out hepatitis
Infection screen (FUO / pre-immunosuppression)	Blood cultures	No growth	No growth	Helps exclude bacteraemia/ Endocarditis
	Malaria test (smear/Ag)	Negative	Negative	Endemic exclusion
	Dengue NS1/IgM	Negative	Negative	Endemic exclusion
	Typhoid testing	Negative	Negative	Endemic exclusion
	HIV, HBsAg, anti-HCV	Negative	Negative	Required baseline before immunosuppression
SLE serology	ANA (IIF)	Negative	1:1280 homogeneous (ASSUMED)	Entry immunologic signal for SLE frameworks
	Anti-dsDNA	Lab-specific	180 IU/mL (pos)	Supports SLE immunologic criterion; activity marker
	C3	90–180 mg/dL	55	Hypocomplementemia supports active immune complex disease
	C4	10–40 mg/dL	7	As above
	aPL panel	Negative	Negative	Important for thrombosis/pregnancy risk stratification
RA serology	Rheumatoid factor	<20 IU/mL	165	High-positive supports RA classification
	Anti-CCP/ACPA	<20 U/mL	240	High-positive; strongly links to erosive RA-like phenotype
Additional autoimmunity (risk stratification)	Anti-Ro/SSA, Anti-La/SSB	Negative	SSA negative	Pregnancy counselling/foetal risk assessment if positive

Evidence base for key interpretive claims: anti-CCP/ACPA is associated with erosive arthritis patterns in SLE-spectrum disease and has been proposed as a marker to identify patients with worse articular prognosis.

Imaging and pathology

Hand/wrist X-ray (PA view): periarticular osteopenia with **early marginal erosions** at MCP 2–3 bilaterally and subtle joint space narrowing; no Jaccoud-type deformities.



Musculoskeletal ultrasound with power Doppler: synovial hypertrophy of wrists and MCPs with Doppler signal consistent with active synovitis; small erosions visualised .

Management and follow-up

Management principles

Treatment must address: 1. **Rapid control of active inflammation** (fever, synovitis) while infection is excluded. 2. **Early DMARD therapy** to prevent erosions (RA paradigm). 3. **Hydroxychloroquine-based lupus foundation** and **glucocorticoid minimisation** (SLE paradigm). EULAR SLE recommendations emphasise HCQ for all, and limiting long-term prednisone-equivalent exposure to low doses with tapering whenever possible. 4. **Treat-to-target monitoring** during active inflammatory arthritis, including reassessment every 1–3 months and therapy adaptation within 3–6 months to achieve remission/low disease activity.

Treatment plan (acute and long-term)

Phase	Therapy	Dose/strategy (ASSUMED; adjust to patient)	Monitoring and safety
Immediate (days 1–14)	Glucocorticoid bridge	Prednisolone 0.5 mg/kg/day (e.g., 25–30 mg/day) with taper plan	Aim rapid taper; avoid prolonged high-dose steroid exposure in lupus strategy frameworks

Phase	Therapy	Dose/strategy (ASSUMED; adjust to patient)	Monitoring and safety
Foundational (start week 1)	Hydroxychloroquine	200 mg BD; ensure ≤5 mg/kg/day actual weight	Baseline ophthalmic evaluation; retinal screening guidance supports ≤5 mg/kg/day dosing to limit toxicity risk
Arthritis control (start week 1–2)	Methotrexate (anchor csDMARD) + folic acid	MTX 15 mg weekly → escalate 20–25 mg weekly if needed; folic acid 5 mg weekly (or per protocol)	CBC/LFT every 2–4 weeks initially; teratogenic—avoid pregnancy; contraception counselling aligns with reproductive health guideline principles
If inadequate response by ~3 months	csDMARD combination or alternative	Add sulfasalazine or switch to leflunomide (avoid if pregnancy planning); consider MTX optimisation and adherence	RA treat-to-target adaptation within 3–6 months recommended
If persistent active disease / erosive progression	Biologic/targeted therapy choice (individualised)	Consider abatacept/rituximab pathways in overlap contexts; avoid reflex TNF inhibitor initiation if lupus activity prominent	Rhupus evidence base is limited; biologic choice must weigh TNF inhibitor–associated lupus-like syndromes risk and SLE activity control
Renal involvement (if class II only)	Renal-protective measures	ACE inhibitor/ARB for proteinuria (if indicated); avoid nephrotoxins	Escalate to MMF/cyclophosphamide only if proliferative nephritis or organ-threatening disease per lupus guidance
Supportive	Bone/GI protection	Calcium + vitamin D; consider bisphosphonate if prolonged steroids; PPI if NSAIDs/steroids	Standard steroid safety care; infection risk counselling

Vaccination and infection screening

Patients with autoimmune inflammatory rheumatic diseases are at increased infection risk due to both disease and immunosuppressive therapy; vaccination strategies and infection screening are therefore core components of safe management.

Vaccination (aligned with ACR and EULAR vaccination guidance): - Prefer **inactivated (non-live) vaccines**, which can generally be administered during immunosuppression; live-attenuated vaccines require caution and timing considerations.

- Ensure age-appropriate immunisations including influenza and pneumococcal; consider HPV vaccination in eligible patients .

Screening/prophylaxis for chronic and opportunistic infections (EULAR): - Screen for **latent tuberculosis** before biologic or targeted synthetic DMARDs, and consider broader screening based on therapy and local epidemiology.

Screen for **hepatitis B and C** prior to immunosuppression escalation; prophylaxis pathways depend on serostatus and planned therapy.

Pregnancy considerations in a 25-year-old

Reproductive counselling is mandated by modern rheumatology standards because multiple DMARDs are teratogenic and disease control strongly influences pregnancy outcomes.

Key elements: - **Preconception:** aim for stable low disease activity; evaluate antiphospholipid antibodies and anti-Ro/SSA/anti-La/SSB for pregnancy risk stratification. - **Medication safety:**

- HCQ is generally compatible with pregnancy and is recommended broadly for lupus.

- Methotrexate is teratogenic; discontinue well in advance per reproductive health recommendations and use effective contraception while on therapy.

Follow-up schedule and prognosis

Suggested follow-up schedule : -2 weeks: symptom response; CBC/LFT (MTX safety); BP/weight; infection review. **6–8 weeks:** disease activity assessment (joint counts, patient-reported outcomes); taper steroids; repeat ESR/CRP. **12 weeks:** treat-to-target decision point—if inadequate improvement, adjust DMARD strategy. Treat-to-target frameworks recommend reassessment every 1–3 months in active disease with adaptation to reach target by 3–6 months.

-3–6 months: evaluate remission/low disease activity; repeat complements/anti-dsDNA and urine quantification if abnormal.

Prognosis from cohort literature: Rhupus cohorts show a distinctive pattern of **more severe RA-associated joint**

involvement (erosions, deformities) with **lower frequency of certain SLE visceral manifestations** compared with SLE controls, though serious SLE organ disease can still occur and must be screened for.

DISCUSSION

Epidemiology and recognition

Rhupus is rare and understandardised: systematic review data emphasise heterogeneity of inclusion criteria and the absence of validated classification and treatment strategies, limiting precise epidemiological estimates. In the largest single-centre cohort frequently cited, rhupus represented **~1.3% of hospitalised SLE patients**, and **all patients** demonstrated erosive imaging abnormalities.

This case is clinically instructive because it began as **FUO**, a frame that often delays rheumatologic synthesis in endemic settings where infectious diseases dominate early decision-making. The explicit dual-criteria approach makes the reasoning transparent and reproducible for peer review.

Pathophysiology and overlap rationale

SLE and RA share partial genetic susceptibility and overlapping immune pathways despite historically distinct immunopathology models. A landmark genetic study demonstrated that STAT4 risk variants increase susceptibility to both RA and SLE, supporting shared autoimmune risk architecture.

Mechanistically, RA is strongly linked with anti-citrullinated protein antibody biology and synovial inflammatory pathways, whereas SLE pathogenesis prominently involves autoantibodies, immune complexes, complement activation, and type I interferon pathway dysregulation. The coexistence of lupus-specific antibodies (anti-dsDNA with low complements) and RA-specific autoimmunity (ACPA/anti-CCP) in the same patient supports a true overlap rather than coincidental positivity, particularly when erosive arthritis is present.

Serology patterns and the “erosive lupus arthritis” problem

Multiple studies identify anti-CCP/ACPA as a marker discriminating erosive arthritis within SLE-spectrum patients: anti-CCP positivity correlates with erosive disease and a more aggressive articular course, and may be accompanied by higher RF/CRP. These data provide biologic plausibility for using anti-CCP/erosions as decision pivots toward RA-grade DMARD intensity in overlap phenotypes.

Treatment dilemmas unique to rhupus

The central dilemma is balancing: - **Early aggressive arthritis control (RA paradigm)** to prevent irreversible erosions, supported by treat-to-target recommendations. - **Steroid-sparing lupus management (SLE paradigm)**: EULAR SLE recommendations emphasise HCQ for all and reducing glucocorticoids to low doses (≤5 mg prednisone-equivalent daily long-term, ideally taper off) while escalating steroid-sparing therapies when targets are not met.

Because rhupus evidence is limited and heterogeneous, management draws from RA and SLE standards rather than rhupus-specific trials. This argues for explicitly documenting disease activity metrics, steroid taper timelines, imaging outcomes, and adverse events in case reports to improve the evidence base...

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