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Severe *Plasmodium vivax* Malaria with Lupus-Mimicking Autoantibodies: A Case Report

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Case Report

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Abstract

Plasmodium vivax infection can present with severe multisystem involvement that overlaps clinically with systemic autoimmune disease. Infection-associated autoantibody production may further complicate diagnostic interpretation.

A 20-year-old man from southeastern Iran presented with one week of high-grade fever with shaking chills, abdominal pain, nausea, and vomiting. Laboratory evaluation demonstrated pancytopenia, rising creatinine, elevated inflammatory markers, and increased lactate dehydrogenase. Initial peripheral blood smear was negative. Despite broad-spectrum antibiotics, fever persisted and routine microbiologic evaluation was unrevealing. Autoimmune screening revealed positive ANA, prompting rheumatology evaluation. Extended serologic testing demonstrated anti-SAE1, anti-RNP A, antiphospholipid antibodies, and borderline anti-Ku, while complement levels remained normal. Although ANA fulfilled the entry criterion for SLE classification, the absence of compatible clinical features and the presence of daily high-grade fevers with prominent rigors argued against immunosuppressive therapy. Progressive cytopenia shifted concern toward hematologic malignancy, and bone marrow examination performed for evaluation of unexplained pancytopenia unexpectedly demonstrated *P. vivax* parasitization. A repeat peripheral smear later demonstrated parasitemia. Antimalarial therapy with artesunate and primaquine was initiated after confirmation and normal G6PD screening. The patient improved rapidly with treatment.

Severe *P. vivax* infection may be accompanied by autoantibodies commonly associated with connective tissue disease in the absence of a compatible clinical phenotype. In endemic settings, malaria should remain in the differential diagnosis of febrile illness with cytopenia, even when serologic findings suggest connective tissue disease.

1. Introduction

Plasmodium vivax has traditionally been considered a cause of benign malaria; however, accumulating evidence has shown that it can cause severe multi-system disease, including hematologic, hepatic, renal, and pulmonary complications (1, 2). This broader clinical spectrum creates diagnostic difficulties, particularly when features overlap with autoimmune conditions.

Malaria and systemic autoimmune diseases, particularly systemic lupus erythematosus (SLE), may overlap clinically through fever, cytopenia, renal dysfunction, elevated inflammatory markers, and autoantibody positivity (3). Malaria can induce transient autoantibodies, including antinuclear and antiphospholipid antibodies, which may falsely suggest an underlying rheumatologic disorder (4). The distinction is important: malaria requires antiparasitic therapy, whereas SLE is treated with immunosuppression. Inappropriate immunosuppressive treatment of unrecognized malaria can worsen outcomes (5).

We present a case of *P. vivax* malaria in a young man from southeastern Iran who developed positive ANA, anti-SAE1, anti-RNP A, and antiphospholipid antibodies, a serologic profile that initially directed the workup toward autoimmune disease and complicated the diagnostic process.

Although transient ANA positivity has been described in infectious diseases (6), the emergence of antibodies typically regarded as relatively specific for connective tissue disease in the setting of acute malaria is rarely reported and may complicate the diagnostic interpretation.

2. Case History

A 20-year-old man from Sistan and Baluchestan Province, a malaria-endemic region in southeastern Iran, presented with a one-week history of high-grade fever with shaking chills, hypogastric pain, nausea, and vomiting. The patient had no significant medical history, recent hospitalizations, blood transfusions, or regular medications.

On admission (day 1), the vital signs were as follows: blood pressure, 110/85 mmHg; heart rate, 100 bpm; respiratory rate, 16/min; temperature, 38°C; and oxygen saturation, 92% on room air. Laboratory investigations revealed pancytopenia (WBC 3.0 × 10^9/L, hemoglobin 13.3 g/dL, platelets 40 × 10^9/L), elevated creatinine (2.1 mg/dL), elevated CRP (132.7 mg/L), and elevated LDH (peaking at 1482 U/L). A peripheral blood smear obtained at admission showed no malaria parasites. Reticulocyte count and liver function tests were normal (Table 1).

Table 1
Serial laboratory findings

Parameter	Day 1	Day 7	Day 10	Day 18	Reference Range
WBC (×10^9/L)	3.0 ↓	4.7	2.4 ↓	4.4	4.5–11.0
Hemoglobin (g/dL)	13.3	9.3 ↓	7.0 ↓	7.2 ↓	13.5–17.5
Platelets (×10^9/L)	40 ↓	70 ↓	30 ↓	160	150–450
Creatinine (mg/dL)	1.0	1.5 ↑	2.1 ↑	1.2	0.7–1.3
LDH (U/L)	—	1400 ↑	1482 ↑	—	140–280
CRP (mg/L)	132.7 ↑	40.3 ↑	—	—	< 10

↓ below the reference range; ↑ above the reference range. Antimalarial treatment initiated on day 11. Day 18 represent the outpatient follow-up.

Initial sepsis evaluation, including blood and urine cultures, was unrevealing, and the infectious diseases consultation found no focal source on examination. Empirical meropenem and vancomycin were initiated; however, fever persisted.

Given the persistent fever with unexplained cytopenia and organ involvement, further evaluation was performed. CT imaging revealed hepatomegaly (150 mm), splenomegaly (132 mm), ascites, and bilateral pleural effusions with lower lobe consolidation. Pro-BNP was elevated (3494 pg/mL; normal < 125), and echocardiography showed a left ventricular ejection fraction of 50% without evidence of endocarditis. Incidental epiploic appendicitis was also observed.

In the absence of an identified infectious source and with multi-system findings, autoimmune screening was performed, and the ANA test was positive. On day seven, a rheumatology consultation was requested, and the patient was transferred for further evaluation of possible SLE. In the rheumatology unit, extended serologic testing was performed to assess the 2019 European League Against Rheumatism/ACR classification framework. The results showed positive F-ANA (titer > 1:100), anti-SAE1, anti-RNP A, anticardiolipin IgM (38.2 U/mL), anti-β2 glycoprotein I IgM antibodies, and borderline anti-Ku. The complement levels (C3 and C4) were within the normal range. Anti-dsDNA antibodies and urinalysis results were normal, further reducing the likelihood of active SLE or lupus nephritis (Table 2).

Table 2
Diagnostic investigations

Investigation	Day	Result	Reference
Peripheral blood smear	1	No parasites	—
Repeat peripheral blood smear	11	*P. vivax* identified	—
Bone marrow aspiration	10	Hypercellular; *P. vivax* in erythroid precursors; hemophagocytosis	—
ANA	5	Positive (> 1:100)	< 1:80
F-ANA	7	Positive (> 1:100)	< 1:80
Anti-SAE1	7	Positive	-
Anti-RNP A	7	Positive	-
Anti-Ku	7	Borderline	-
Anti-dsDNA	7	Negative	-
C3 (mg/dL)	7	85	75–135
C4 (mg/dL)	7	26.2	10–40
Anticardiolipin IgM (U/mL)	7	38.2	< 20
Anti-β2 glycoprotein I IgM (U/mL)	7	16	< 10
Pro-BNP (pg/mL)	3	3494	< 125
Blood and urine cultures	Multiple	No growth	—
G6PD screen	11	Normal	—

3. Methods

Despite this serological profile, the evolving fever pattern, clearly quotidian high-grade episodes accompanied by prominent shaking chills, and the absence of mucocutaneous, musculoskeletal, or other classification features of connective tissue disease argued against the initiation of immunosuppressive therapy. Because the antibody constellation was unexpected in this clinical context, the panel was repeated and again demonstrated persistent positivity for the same autoantibodies.

By day 10, progressive pancytopenia (WBC 2.4 × 10^9/L, hemoglobin 7.0 g/dL, platelets 30 × 10^9/L) and ongoing systemic symptoms shifted the concern toward hematologic malignancy. Bone marrow aspiration was performed to evaluate unexplained cytopenia and to exclude malignancy. Examination

revealed hypercellular marrow with *P. vivax* parasites in erythroid precursors and evidence of hemophagocytosis (Table 2, Fig. 1).

4. Conclusion and Results

A repeat peripheral blood smear on day 11 revealed *P. vivax* parasites. After confirming the bone marrow findings and normal G6PD screening results, antimalarial therapy with intravenous artesunate and oral primaquine was initiated on day 11.

The patient rapidly improved after treatment. The fever and abdominal pain resolved within 48 hours. He was discharged on day 14 in stable condition. Follow-up on days 17–18 demonstrated progressive improvement, indicating hematologic recovery (WBC = 4.4 × 10^9/L, Hb = 7.2 g/dL, PLT = 160 × 10^9/L) and his serum creatinine began to normalize (1.2 mg/dL).

3. Discussion

P. vivax infection is increasingly recognized as capable of producing severe multi-system diseases (7, 8). In this case, fever, renal dysfunction, pulmonary involvement, and profound cytopenia were consistent with complicated vivax malaria. The diagnostic difficulty arose not from the severity alone but from a serologic profile that closely resembled that of a systemic autoimmune disease.

The initial peripheral blood smear was also negative. In the setting of persistent fever and progressive pancytopenia, autoimmune evaluation revealed ANA positivity along with anti-SAE1, anti-RNP A, anti-Ku, and antiphospholipid antibodies. This constellation would ordinarily prompt consideration of dermatomyositis, mixed connective tissue disease, antiphospholipid syndrome, or SLE (9, 10). Although this serologic constellation suggested connective tissue disease, the absence of compatible clinical features and the presence of quotidian fevers with shaking chills argued against immunosuppressive therapy. Progressive pancytopenia subsequently shifted the differential diagnosis toward hematologic malignancy, prompting bone marrow examination. The discordance between disease-associated serology and the absence of a compatible clinical phenotype is central to this case.

Transient ANA and antiphospholipid antibodies are well described in malaria and are generally attributed to polyclonal B cell activation during acute infection (4, 11). The appearance of antibodies regarded as relatively disease-specific, particularly anti-SAE1 and anti-RNP A, is less commonly reported. We found no prior reports of anti-SAE1 positivity in malaria, though similar transient positivity has been observed in severe COVID-19 (12, 13).

Severe malaria is characterized by intense immune activation, nucleic acid sensing, oxidative stress, apoptosis, and substantial bone marrow turnover (14, 15). Anti-RNP targets RNA-processing complexes, anti-Ku recognizes DNA repair proteins exposed during cellular stress, and anti-SAE1 is directed against components of the SUMOylation pathway involved in stress responses and host–pathogen interactions (16). While direct mechanistic evidence linking *P. vivax* to these specific antibodies is lacking, the

immunologic milieu of severe infections provides a plausible environment for transient autoreactivity beyond conventional ANA patterns.

Importantly, the reported specificity of many autoantibodies is derived from comparisons between patients with established autoimmune diseases and healthy controls. Acute patients with systemic infections are rarely represented in such validation cohorts. This case does not negate the clinical value of serologic specificity; rather, it illustrates that specificity estimates derived from selected validation cohorts may not fully apply to acutely infected patients with profound immune activation.

The subsequent clinical course clarified the underlying etiology. Bone marrow examination demonstrated *P. vivax* parasites with hemophagocytosis (17), and initiation of artesunate and primaquine led to rapid defervescence and hematologic recovery without immunosuppressive therapy. No rheumatological manifestations were observed during the follow-up period. The temporal relationship between parasite clearance and clinical improvement supports infection-associated immune activation rather than primary autoimmunity.

Hematological findings further highlight the systemic impact of severe vivax infections. Although anemia and thrombocytopenia are common in malaria, marked pancytopenia suggests significant bone marrow involvement (18, 19). The accumulation of parasites within erythroid precursors may limit peripheral parasitemia and contribute to dyserythropoiesis, offering a plausible explanation for the initial smear negativity (20). In this case, marrow examination established the diagnosis before peripheral smear conversion, underscoring that a single negative smear does not exclude malaria in endemic settings.

Follow-up autoimmune serology was not performed to confirm the normalization of antibody titers after treatment. Species identification relied on morphology rather than PCR confirmation. Although bone marrow hemophagocytosis was observed, triglyceride and fibrinogen levels were unavailable, limiting the formal assessment of hemophagocytic lymphohistiocytosis. The patient was lost to long-term follow-up, which precluded the assessment of relapse or the later emergence of autoimmune diseases.

4. Conclusion

This case illustrates that severe *P. vivax* infection may be accompanied by autoantibodies typically associated with connective tissue diseases, even in the absence of a compatible clinical phenotype. When serological findings and clinical presentations diverge, careful attention to the disease course and alternative etiologies remains essential. In endemic settings, malaria should remain in the differential diagnosis of febrile illness with cytopenia, even when peripheral smears are initially negative and autoimmune serology results are positive. The clinical phenotype remains decisive.

Declarations

Author Contributions

Mandana Khodashahi: conceptualization, data curation, investigation, project administration, supervision, validation, writing – review and editing. **Muhammed Joghatayi:** conceptualization, data curation, investigation, project administration, validation, visualization, writing – original draft, writing – review and editing. **Pejman Hosseinzadeh:** data curation, investigation, validation, writing – original draft. **Maryam Najafı Nodeh:** data curation, investigation, writing – review and editing.

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Ethical Statement

This case report was conducted in accordance with the principles of the Declaration of Helsinki. All efforts were made to maintain the patient's privacy and confidentiality.

Consent for Publication Declaration

Written informed consent was obtained from the patient for publication of this case report and any accompanying images. A copy of the written consent is available for review by the Editor-in-Chief of this journal.

Conflict of Interest

The authors declare no conflict of interest.

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Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analyzed during the current study.

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Figures

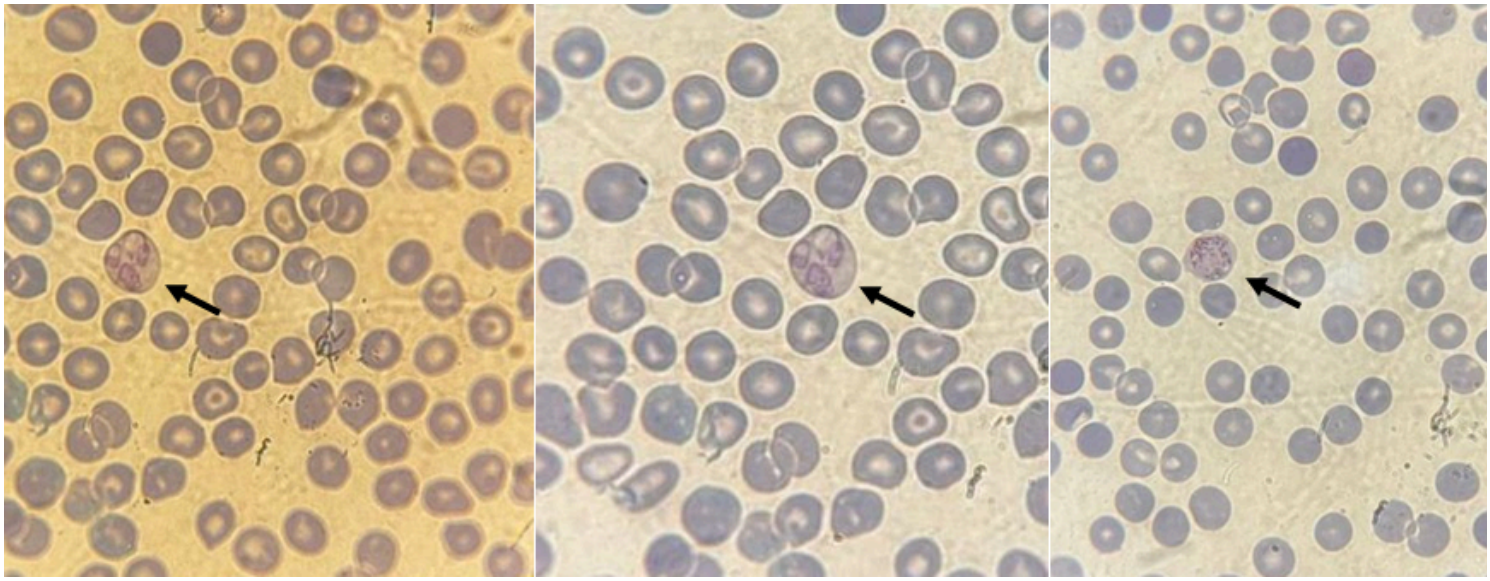


Figure 1

Plasmodium vivax parasites observed in bone marrow aspirate using Wright–Giemsa staining.