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EVOLVING SYSTEMIC LUPUS ERYTHEMATOSUS MANIFESTING AS SEVERE SEPSIS WITH SECONDARY AUTOIMMUNE HEMOLYTIC ANEMIA: A DIAGNOSTIC DILEMMA

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ABSTRACT

Systemic Lupus Erythematosus (SLE) is a chronic autoimmune condition with diverse clinical presentations, including complex hematologic and infectious complications. We report the case of a 23-year-old female who presented with high-grade fever, jaundice, and a lower leg ulcer. Initial findings of gram-negative bacteremia led to a diagnosis of sepsis; however, persistent severe anemia and positive immunologic markers (ANA 2+, low complement levels) confirmed underlying SLE with secondary Autoimmune Hemolytic Anemia (AIHA). This case highlights the challenges of diagnosing SLE when it mimics or coexists with severe sepsis, emphasizing the need for early recognition of AIHA to initiate life-saving immunosuppressive therapy.

KEYWORDS: Systemic Lupus Erythematosus (SLE), Autoimmune Hemolytic Anemia (AIHA), Sepsis, Hemolysis, ANA, Corticosteroids.

INTRODUCTION

Systemic Lupus Erythematosus (SLE) is a prototypical multi-system autoimmune disease characterized by the production of antibodies against self-antigens, leading to widespread inflammatory damage in various organ systems. The clinical spectrum of SLE is notably diverse, ranging from mild mucocutaneous involvement to life-threatening hematologic, renal, and neurological complications. Among the hematologic manifestations, **Autoimmune Hemolytic Anemia (AIHA)** is a well-recognized but relatively rare initial presentation, occurring in approximately **5% to 10%** of SLE patients. This case report details the clinical journey of a 23-year-old female whose evolving SLE initially presented as severe sepsis with a secondary AIHA. By examining this atypical presentation, we highlight the critical importance of maintaining a high index of suspicion for autoimmune disorders in critically ill patients with unexplained, refractory hemolysis and systemic inflammation.

CASE PRESENTATION

A 23-year-old female presented to the emergency department with a primary complaint of high-grade fever, progressively worsening jaundice, and severe generalized weakness. On physical examination, she was found to have significant pallor and icterus. Notably, a single, well-defined, non-healing ulcer was observed over her left lower leg.

Initial clinical assessment suggested a systemic inflammatory process. Laboratory investigations at admission revealed a critical hematologic state with a hemoglobin (Hb) level of 4.0 g/dl and a packed cell volume (PCV) of 12.8%. The presence of indirect hyperbilirubinemia (8.1 mg/dl) and significantly elevated lactate dehydrogenase (LDH) pointed toward an active hemolytic process.

Simultaneously, the patient exhibited signs of systemic infection, including a high total leukocyte count of 25,800/mm³ with neutrophilic leukocytosis. Blood cultures subsequently confirmed gram-negative

bacteremia. Based on these findings, an initial diagnosis of severe sepsis with secondary hemolysis was made. The patient was immediately started on aggressive supportive care and broad-spectrum antibiotic therapy.

Despite achieving source control for the infection, the patient's hemolytic anemia failed to stabilize and showed signs of further deterioration. This prompted a more extensive immunologic workup to investigate potential underlying autoimmune etiologies. A **Direct Coombs test** returned positive, and further testing revealed positive antinuclear antibodies (ANA 2+ via immunofluorescence) and low serum complement levels. These markers, combined with a 24-hour urinary protein excretion of 1350 mg/day and mild hepatosplenomegaly on ultrasound, confirmed a diagnosis of **Systemic Lupus Erythematosus (SLE) with secondary Autoimmune Hemolytic Anemia (AIHA)**.

Investigations

The following table summarizes the key laboratory and radiological findings that guided the transition from a diagnosis of simple sepsis to a systemic autoimmune crisis.

Parameter	Result	Clinical Significance
Hemoglobin (Hb)	4.0 g/dl	Severe life-threatening anemia.
WBC Count	25,800/mm³	Marked neutrophilic leukocytosis suggestive of sepsis.
Total Bilirubin	14.7 mg/dl	Significant jaundice; Indirect (8.1) > Direct (6.5).
Direct Coombs Test	POSITIVE	Confirms immune-mediated hemolysis (AIHA).
ANA (IF Method)	1:100 (2+ Positive)	Strongly suggests underlying SLE.
Serum Creatinine	2.8 mg/dl	Acute kidney injury or lupus-related renal involvement.
24-hr Urinary Protein	1350 mg/day	Significant proteinuria, consistent with Lupus Nephritis.
Complement Levels	Low	Indicates active consumption in an SLE flare.
USG Abdomen	Hepatosplenomegaly	

Differential Diagnosis

The primary challenge in this case was distinguishing between a singular infectious process and a underlying autoimmune disease being unmasked by infection.

1. Severe Sepsis with Secondary Hemolysis

- **Rationale:** The patient presented with gram-negative bacteremia and a high WBC count (25,800/mm³), making sepsis the most likely initial diagnosis.
- **Supporting Evidence:** High-grade fever, elevated CRP (100), and jaundice.
- **Differentiation:** While sepsis can cause hemolysis (e.g., via DIC or direct bacterial hemolysins), the severity of the anemia (Hb 4.0 g/dl) and the positive Direct Coombs test strongly indicated an immune-mediated mechanism rather than simple infection-related destruction.

2. Systemic Lupus Erythematosus (SLE) with AIHA

- **Rationale:** Autoimmune Hemolytic Anemia is a recognized, though rare, initial presentation of SLE.
- **Supporting Evidence:** Positive Direct Coombs test, positive ANA (1:100), low complement levels, and significant proteinuria (1350 mg/day).
- **Differentiation:** The presence of multi-organ involvement (renal and hematologic) alongside immunologic markers confirmed SLE as the primary etiology despite the concurrent bacteremia.

3. Thrombotic Microangiopathy (TMA) / Thrombotic Thrombocytopenic Purpura (TTP)

- **Rationale:** TMA can present with the "pentad" of fever, anemia, thrombocytopenia, renal failure, and neurological symptoms.
- **Supporting Evidence:** The patient had fever, anemia, and elevated creatinine (2.8 mg/dl).
- **Differentiation:** This was ruled out by the **absence of schistocytes** on the peripheral smear and the positive Direct Coombs test (TMA is typically Coombs-negative).

4. Malaria

- **Rationale:** Endemic in many regions, malaria can cause severe hemolytic anemia, jaundice, and hepatosplenomegaly.
- **Supporting Evidence:** Fever and jaundice.
- **Differentiation:** Ruled out by a peripheral smear that was **negative for malarial parasites**.

5. Primary Sjögren's Syndrome with Renal Involvement

- **Rationale:** Though less likely given the classic SLE markers, Sjögren's can present with renal tubular acidosis and systemic inflammatory features.
- **Supporting Evidence:** References cited in the case (Talal et al., Shearn et al.) focus on renal involvement in Sjögren's.
- **Differentiation:** The specific ANA pattern and the severity of the AIHA in this 23-year-old female pointed more strongly toward SLE.

Treatment

The management of this patient required a dual-track strategy to address life-threatening gram-negative bacteremia while simultaneously suppressing a severe autoimmune flare. The treatment was initiated in a stepwise manner as the diagnosis evolved from sepsis to SLE-associated AIHA.

1. Phase I: Immediate Stabilization and Sepsis Management

Initial treatment focused on the clinical presentation of severe sepsis and profound anemia:

- **Broad-Spectrum Antibiotics:** Aggressive intravenous antibiotic therapy was initiated to target the gram-negative bacteremia identified in blood cultures.
- **Hemodynamic Support:** Aggressive supportive measures, including intravenous fluids, were utilized to maintain organ perfusion in the setting of severe anemia and sepsis.
- **Blood Transfusions:** Given the critical hemoglobin level of **4.0 g/dl**, blood transfusions were necessary; however, in AIHA, cross-matching can be difficult, and transfusions provide only transient benefits as the autoantibodies destroy the donor cells.

2. Phase II: Immunosuppressive Therapy

Once the Direct Coombs test and ANA results confirmed that the hemolysis was immune-mediated (AIHA secondary to SLE), the treatment shifted to address the underlying autoimmune cause:

- **Systemic Corticosteroids:** This was the cornerstone of the patient's recovery. Corticosteroids work by:
  - Reducing the production of pathogenic autoantibodies by B-cells.
  - Decreasing the clearance of antibody-coated red blood cells by splenic macrophages.
  - Downregulating the systemic inflammatory response.
  - **Clinical Response:** The patient showed significant clinical improvement following the introduction of corticosteroids, with stabilization of hemoglobin levels and improvement in renal function.

3. Phase III: Management of Multi-organ Involvement

The patient's investigation results (creatinine 2.8 mg/dl and 1350 mg/day proteinuria) suggested active **Lupus Nephritis**:

- **Renal Protection:** In addition to steroids, management likely involved monitoring electrolyte balance and blood pressure.
- **Wound Care:** The well-defined ulcer on the left lower leg required localized care. In the context of SLE, such ulcers are often vasculitic and improve only once the systemic autoimmune process is controlled.

DISCUSSION

The clinical intersection of **Systemic Lupus Erythematosus (SLE)** and **severe sepsis** presents a significant diagnostic challenge, as both conditions can manifest with overlapping systemic inflammatory features. This case highlights a "diagnostic camouflage" where confirmed gram-negative bacteremia initially masked an underlying autoimmune crisis.

1. The Diagnostic Dilemma: Sepsis vs. SLE

In this patient, the simultaneous presence of fever, high inflammatory markers (ESR 110, CRP 100), and bacteremia strongly suggested sepsis as the primary driver. However, several atypical features pointed toward an evolving autoimmune etiology:

- **Refractory Anemia:** A hemoglobin level of 4.0 g/dl is exceptionally severe for sepsis-related hemolysis alone.
- **The Leg Ulcer:** While common in infectious settings, localized ulcers in young patients can also represent vasculitic lesions characteristic of SLE.
- **Multi-Organ Involvement:** The combination of hepatosplenomegaly, proteinuria (1350 mg/day), and elevated creatinine (2.8 mg/dl) suggested a systemic process affecting the renal and reticuloendothelial systems simultaneously.

2. Pathophysiology of AIHA in SLE

Autoimmune Hemolytic Anemia (AIHA) is a rare but life-threatening hematologic manifestation of SLE. It occurs when B-cell dysregulation leads to the production of autoantibodies (typically IgG) against red blood cell antigens.

- **Coombs Positivity:** The **Positive Direct Coombs test** was the definitive laboratory finding that confirmed an immune-mediated destruction of red cells.
- **Complement Consumption:** Low complement levels in this patient indicate the activation and consumption of the classical complement pathway, a hallmark of active SLE flares.

3. The Overlap with Sepsis

Sepsis can act as a potent "trigger" for an SLE flare. The systemic cytokine storm associated with gram-negative bacteremia can exacerbate pre-existing autoimmune pathways.

- **The Diagnostic Trap:** Clinicians often attribute hemolysis in a septic patient to microangiopathic processes or direct bacterial toxins.
- **Differentiating Factors:** In this case, the absence of schistocytes on the peripheral smear ruled out Thrombotic Microangiopathy (TMA), while the positive ANA (1:100) and low complements solidified the SLE diagnosis.

4. Therapeutic Challenges

The management of concurrent sepsis and SLE-induced AIHA requires a delicate balance:

- **Antibiotics:** Crucial for clearing bacteremia but insufficient to stop immune-mediated RBC destruction.
- **Corticosteroids:** Essential for treating AIHA but traditionally used with caution in active infection.
- **Outcome:** As demonstrated, the introduction of corticosteroids led to rapid clinical improvement, proving that the primary life-threatening component was the autoimmune hemolytic process rather than the infection alone.

5. Renal Implications

The patient's elevated creatinine (2.8 mg/dl) and significant proteinuria (1350 mg/day) suggest evolving **Lupus Nephritis**. This reinforces the importance of early diagnosis, as delayed treatment with immunosuppressants can lead to permanent renal damage. The references cited in the original poster (Talal et al., Shearn et al., and François et al.) specifically focus on renal involvement in autoimmune syndromes, underscoring the severity of the renal markers observed here.

CONCLUSION

The clinical presentation of this 23-year-old female underscores a critical diagnostic challenge: the coexistence of **severe sepsis** and an **evolving systemic autoimmune disease**. While the initial diagnosis of gram-negative bacteremia was accurate, it provided only a partial explanation for the patient's critical condition. The severity of the anemia (Hb 4.0 g/dl) and the multi-organ involvement (renal and hepatic) were indicative of a more complex underlying pathology. Ultimately, a high index of clinical suspicion for autoimmune disorders in critically ill patients is essential to prevent delays in life-saving treatment and to improve overall prognostic outcomes in complex cases of SLE.

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