

# Autoimmune hemolytic anemia as an initial presentation in children with systemic lupus erythematosus: two case reports

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## Abstract

We report the cases of two children who presented with autoimmune hemolytic anemia (AIHA) as an initial presentation of systemic lupus erythematosus (SLE). Both patients had a positive Coombs test, anemia, and an increased number of spherocytes in their blood smear. The patient in Case 1 presented with fever, urticarial erythema, facial paresis, AIHA, and leucopenia. Immunological screening revealed low complement protein levels and positive anti-nuclear antibody, anti-double-stranded DNA, and antiphospholipid antibody results. A further laboratory workup revealed a positive lupus anticoagulant (LA) result and low factor II levels. She was diagnosed with lupus anticoagulant hypoprothrombinemia syndrome (LAHPS) in addition to SLE. The patient in Case 2 presented with fever, butterfly rash, thyroid enlargement, leucopenia, and AIHA. She was diagnosed with SLE with thyroiditis. Both patients were started on combined immunosuppressive therapy, and both patients' clinical symptoms finally resolved. A literature review on childhood SLE showed that AIHA is common in patients with SLE. LAHPS is an uncommonly identified cause of bleeding in patients with SLE, and it must be considered when evaluating children with a positive LA result.

## Keywords

Autoimmune hemolytic anemia, systemic lupus erythematosus, factor II deficiency, lupus anticoagulant hypoprothrombinemia syndrome, antiphospholipid syndrome, children

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## Introduction

Systemic lupus erythematosus (SLE) is a complex autoimmune disease with variable clinical features.<sup>1</sup> Clinical manifestations are associated with many autoantibodies, ensuing immune complex formation and deposition, and other immune processes.<sup>2,3</sup> Hematological abnormalities are common in children with SLE, with an incidence of 34% to 82.7%.<sup>4</sup> Anemia, thrombocytopenia, and leucopenia are common hematological manifestations in pediatric SLE patients.<sup>4</sup> Hematological involvement may result from bone marrow failure or excessive peripheral cell destruction, both of which may be immune-mediated.<sup>5</sup> Hematological abnormalities develop at the time of diagnosis and throughout the course of the disease. Knowledge and awareness of patients with hematological involvement are essential for making an appropriate diagnosis and management.

Autoimmune hemolytic anemia (AIHA) a classification criteria for SLE.<sup>2</sup> The mechanism is thought to be caused by the destruction of red blood cells through warm or cold antibodies.<sup>6</sup> Patients with AIHA may present with symptoms of anemia or hemolysis or symptoms of an underlying disorder. Severe hemolysis may lead to hepatosplenomegaly, hemoglobinuria, and signs of heart failure.<sup>7</sup> Managing patients with AIHA may be challenging because specific therapy should be individualized in accordance with the disease manifestations and its severity.<sup>8</sup>

Here, we report the cases of two patients who both initially presented with AIHA but were finally diagnosed with SLE. One patient presented with prolonged bleeding, and further investigation revealed a positive Lupus anticoagulant (LA) result and low factor II levels. She was diagnosed with SLE-related LA hypoprothrombinemia syndrome (LAHPS), with the presence of LA and factor II deficiency. Both patients

were treated with combined immunosuppressive therapy, and their symptoms resolved after follow-up.

## Case report

### Case 1

A 4-year-old girl was referred to the hospital for progressive pallor and intermittent fever (high grade) for 1 month. One month previously, the girl had attended a local hospital clinical department for pallor, and she was found to have anemia, with a hemoglobin level of 64 g/L. She was suspected of having iron deficiency anemia, and iron proteinsuccinylate oral solution was prescribed for 4 weeks. However, the anemia did not improve. Two days before attending our hospital, she returned to the local hospital for epistaxis and melena. A blood test revealed that her anemia had worsened, with a hemoglobin level of 39 g/L, an abnormal coagulation test, and prolonged activated partial thromboplastin time (APTT) and prothrombin time (PT). The fecal occult blood result was weakly positive. She then attended our hospital. On examination, she had a high fever of 39.8°C, marked pallor, hepatosplenomegaly, several ecchymoses over the lower and upper extremities, back, and abdomen, as well as joint swelling in the left foot, swelling and red spots in the parotid duct mucosa, and urticarial erythema on her face. There was left facial weakness upon crying, and she could not completely close her left eyelid while sleeping. The initial laboratory investigation revealed severe anemia, leucopenia, and reticulocytosis (Table 1). Her urinalysis and kidney function test results were normal without proteinuria. A coagulation test revealed prolonged PT and APTT (Table 2). Blood and pharynx swab cultures were all sterile. Serology for human immunodeficiency virus (HIV) was negative. Hepatitis B

**Table 1.** Basic laboratory investigations in our patients with systemic lupus erythematosus and anticoagulant hypoprothrombinemia syndrome.

Laboratory test	Case 1	Case 2	Normal range
Hemoglobin (g/L)	28	81	115–150
Hematocrit	0.094	0.244	0.35–0.45
White cell count ( $\times 10^9/L$ )	2.0	2.6	3.5–9.5
Platelets ( $\times 10^9/L$ )	120	204	125–350
Direct Coombs test	+	+	–
Reticulocytes (%)	12.03	1.65	0.5–1.5
Absolute reticulocyte count ( $\times 10^9/L$ )	119.5	54.9	24–84
Total bilirubin	10.9	9.7	3.4–20.5
Direct bilirubin	6.4	2.5	1–20.1
LDH	337		97–350
ANA	1:320	1:320	<1:100
Anti-dsDNA antibody	831.99	300	<100
Anti-sm antibody	–	–	–
Anti-Ro/SS-A antibody	–	–	–
Anti-La/SS-B antibody	–	–	–
Anti-RNP antibody	–	–	–
C3 (mg/dL)	0.08	0.407	0.85–1.93
C4 (mg/dL)	0.02	0.043	0.12–0.36

LDH, lactate dehydrogenase; ANA, antinuclear antibody; C3, complement 3; C4, complement 4; anti-RNP, anti-ribonucleoprotein.

**Table 2.** Coagulation studies in our patient with systemic erythematosus and lupus anticoagulant hypoprothrombinemia syndrome.

Laboratory test	Pretreatment	Post-treatment (2 months)	Reference range
Factor II level (%)	2.7	NA	50–150
LA	+	–	–
PT (s)	41.3	9.5	10–14
aPTT (s)	116.4	24.4	25–31.3
aCL IgM (MPL)	87.83	NA	<40
aCL IgG (GPL)	37.52	NA	<40

The plasma-mixing test indicated LA, which was confirmed using aPTT-LA and dilute dRVVT. aCL, anticardiolipin; LA, lupus anticoagulant; PT, prothrombin time; aPTT, thromboplastin time; Ig, immunoglobulin; dRVVT, Russell's viper venom time; NA, not available.

surface antigen was not detectable. A toluidine red unheated serum test for anti-syphilis showed weakly positive results. Serum calcium levels were low (1.68 mmol/L), and direct and indirect Coombs test results were both positive. From the blood smear, there was an increased number of spherocytes, which indicated an autoimmune hemolytic process.

Brain magnetic resonance imaging was performed to investigate the patient's left facial paresis, and the results did not show any cerebral lesions or ischemic events. A further cerebrospinal fluid examination was also negative. Morphology and immunophenotyping of bone marrow aspirates excluded acute leukemia and

hemophagocytosis. She was diagnosed with upper respiratory infection with fever, swelling, and red spots on the parotid duct mucosa as well as with leucopenia. Coagulation dysfunction and severe anemia were also suspected because there was gastrointestinal bleeding and hemorrhagic anemia. Treatment with intravenous antimicrobials (amoxicillin potassium clavulanate) was initiated. Supportive therapy including red blood cells, plasma and calcium gluconate was also administered. However, there was no improvement in bleeding manifestations and gum bleeding, and epistaxis recurred. Further clinical manifestations included a small amount of dark red edema around the nasal tip and lower jaw and scattered pigmentation on the face. The patient's medical history revealed repeated malar rashes on her face in the past 6 months. Because there was multisystem involvement and urticarial erythema, autoimmune diseases were suspected, and immunologic tests were performed. The immunological screening results were positive for antinuclear antibody (ANA) (1:320), anti-double-stranded DNA (anti-dsDNA), anti-histones, and anti-nucleosomes. She had low serum C3 and C4 complement factors, and LA and anticardiolipin antibody results were positive. Coagulation factor assays found that factor II was significantly reduced (2.7%).

The presence of fever, urticarial erythema, AIHA, leucopenia, low complement proteins, and positive ANA, anti-dsDNA, and antiphospholipid antibodies suggested a diagnosis of SLE in accordance with the 2019 European League Against Rheumatism/American College of Rheumatology classification criteria for SLE. The patient presented with positive LA and low coagulation factor II, and a diagnosis of SLE with LAHPS was made. She was started on oral prednisone 1.5 mg/kg/day and mycophenolate mofetil (MMF) 15 mg/kg/day. She responded well to the treatment, and the bleeding manifestations

subsided. Three days after treatment, her white blood cell count was within the normal range. After 2 months of follow-up, her hemoglobin level was increased to 125 g/L, and the coagulation test results were within the normal range (Table 2).

## Case 2

An 11-year-old girl was referred to our hospital for intermittent fever, fatigue, and poor appetite for 3 weeks. She had a history of ankle joint tenderness and had lost approximately 5 kg of weight in the previous 1.5 months. She had previously attended a local hospital, where blood test results showed leucopenia, anemia, and increased C-reactive protein levels (9 mg/L), and she was started on antibiotics. However, her fever remained high (40.5°C) without improvement. She was suspected of having an autoimmune disease. A further thyroid function investigation revealed abnormalities. She was then referred to our hospital. Physical examination showed a mild fever (37.6°C), pallor, butterfly rash, and thyroid enlargement (grade II). There was no joint swelling or tenderness. Blood test results revealed leucopenia, anemia, and a normal reticulocyte count after correction ( $54.9 \times 10^9/L$ ). A direct Coombs test result was also positive (Table 1). Blood smear results showed that there was an increased number of spherocytes that confirmed the diagnosis of AIHA. Further pathogen workup excluded infectious disease. Thyroid function showed increased triiodothyronine (1.92 µg/L), thyroxine (168.2 µg/L), thyroid peroxidase antibody (136.8 kU/L), and thyroglobulin antibody (>500 kU/L) levels and normal thyroglobulin antibody (5.104 mIU/L) levels. The autoimmune workup was performed using an enzyme-linked immunosorbent assay, and the results were positive for ANA, anti-dsDNA, anti-ribonucleoprotein, anti-nucleosome, and anti-histone antibodies.

Serum C3 and C4 complement factor levels were low. Bone marrow examination excluded acute leukemia, aplastic anemia, and hemophagocytosis. The colonoscopy excluded colonic lesions, and the patient had a medical history of poor appetite and weight loss. She was diagnosed with SLE with fever, butterfly rash, leucopenia, AIHA, low complement proteins, and positive ANA and anti-dsDNA results. The patient was started on prednisolone 1 mg/kg/day and leflunomide tablets 0.3 mg/kg/day. Our patient responded to the treatment with clinical improvement and normal cell counts 1 week later. A follow-up 2 weeks later revealed abnormal hepatic function, with increased aspartate transaminase (ALT), alanine transaminase (AST), and gamma-glutamyltransferase levels. Her alkaline phosphatase, total bilirubin, total protein, and albumin levels were within the normal range. She was considered to have adverse drug effects, so leflunomide was stopped and substituted with MMF 15 mg/kg/day. Liver-protecting drugs including compound glycyrrhizin and reduced glutathione sodium were also used. Her ALT and AST levels were normal at the 1-month follow-up. She has been followed-up for 1.5 years, and the prednisolone was tapered to 12.5 mg/day. She is clinically well with normal cell counts.

Written informed consent for the publication of this report was obtained from the patients' patients or their families. The reporting of this case conforms to the CARE guidelines.<sup>9</sup>

## Discussion

SLE is a multisystemic, inflammatory, heterogeneous autoimmune disease.<sup>1</sup> It is characterized by simultaneous or sequential organ and systemic involvement, with unpredictable flares and high mortality.<sup>8,10</sup> It is rare in children, but pediatric patients have a more severe clinical course

compared with that seen in adults, and there is a higher prevalence of lupus nephritis and hematologic anomalies in pediatric patients compared with those in adults.<sup>11,12</sup> The presentation and clinical courses are variable among different ages at disease onset. Thus, making a diagnosis can be challenging.<sup>13</sup> Here, we report the cases of two patients who presented with AIHA and were finally diagnosed with SLE.

There is a diverse spectrum of hematological involvement in SLE. Hemolytic anemia, leucopenia, lymphopenia, and immune-mediated thrombocytopenia are frequently seen in patients with SLE.<sup>14</sup> AIHA is a clinical diagnostic criterion for SLE.<sup>2</sup> The diagnosis is confirmed with a positive direct antiglobulin test, or Coombs test, and laboratory evidence of hemolysis, including anemia, elevated lactate dehydrogenase, indirect bilirubin, and reticulocyte count. Hemolytic anemia can occur years before or after a SLE diagnosis is made, and there is rarely an initial presentation of SLE.<sup>15</sup> It occurs as part of the SLE flare with or without leucopenia and thrombocytopenia. The mechanism is thought to be mediated by autoantibodies against red blood cells. Erythrocytes coated with immunoglobulin G antibodies undergo membrane changes as they pass through the spleen, and the resulting spherocytes are removed by phagocytosis.<sup>15</sup> The Coombs test or direct antiglobulin test is used to screen for erythrocyte antibodies, and positive results are common in patients with SLE.<sup>16</sup> Clinically, AIHA can range from mild hemolysis with compensatory reticulocytosis to rapid, life-threatening hemolysis resulting in hemodynamic compromise. Patients with active hemolysis are at an increased risk of thrombotic events.<sup>17</sup> SLE patients with AIHA are usually associated with severe lupus, affecting major organs and causing end-organ damage.<sup>18</sup> It is a condition with distinct features characterized by a higher prevalence and severity in

children and concomitant constitutional symptoms, including higher fever and more weight loss and hepatosplenomegaly than those in adults.<sup>3</sup> AIHA may be the first manifestation of SLE and can appear several years before a diagnosis of SLE is made.<sup>15</sup> Both of our patients initially presented with AIHA as indicated by a positive direct Coombs test result and the increased number of spherocytes on blood smears. It is suggested that for patients who present with AIHA and multisystem involvement, a full workup for autoimmune diseases such as SLE should be conducted.

Bleeding in SLE may occur due to thrombocytopenia, infection with disseminated intravascular coagulation, and macrophage activation syndrome. The incidence of LA in association with SLE is reported to be 20% to 40%.<sup>19</sup> LA is highly associated with thrombosis rather than bleeding events. Bleeding symptoms in a patient with LA may rarely be caused by coexisting specific antibodies against prothrombin (factor II). The presence of factor II deficiency, which is suspected on the basis of prolonged PT and APTT, along with LA positivity is known as LAHPS. It is rare, with just over 100 reported cases to date.<sup>20</sup> This anti-prothrombin antibody causes accelerated clearance of prothrombin, resulting in hypoprothrombinemia,<sup>21</sup> and lupus patients can develop various degrees of bleeding, ranging from mild mucocutaneous bleeding to severe life-threatening hemorrhage, such as pulmonary hemorrhage and adrenal hemorrhage, especially if the factor II level falls below 10%.<sup>22</sup> Pilia et al. performed a review of 32 pSLE cases with LAHPS in 2018, and the median age of presentation was 12 years, and most were female patients. Skin bleeds (50%) and epistaxis (37.5%) were the most common clinical presentations.<sup>23</sup> Among our patients, one presented without hemorrhage, so the coagulation test was not evaluated. The other patient

presented with prolonged epistaxis, ecchymosis, and gum bleeding with positive LA test results. Her coagulation test revealed prolonged PT and APTT and low factor II levels. We did not perform an anti-prothrombin antibody test because it was not available at our hospital, it is suggested for patients with prolonged bleeding, and careful laboratory evaluation should be performed. For the LAHPS diagnosis, a variety of tests including the coagulation factor II test should be performed in suspected cases. To the best of our knowledge, among all similar reported cases, the cases reported herein represent the youngest children diagnosed with SLE-related LAHPS published to date.

There is no consensus or evidence-based guideline for AIHA treatment in pediatric SLE. AIHA therapy is mostly based on isolated case reports and a few retrospective studies.<sup>7</sup> Specific immunosuppressive therapy should be customized for each patient on the basis of disease manifestations and severity, and we should control disease activity and minimize drug-induced adverse events. First-line treatment includes corticosteroids in the form of pulsed intravenous methylprednisolone or high-dose oral prednisone. Steroid-sparing agents include hydroxychloroquine, MMF, azathioprine, cyclophosphamide, rituximab, and tacrolimus.<sup>17</sup> Supportive care, such as fresh frozen plasma, platelets, factor concentrate, and packed red blood cells, is also suggested for children with severe bleeding.<sup>20</sup> In both of our patients, to minimize the corticosteroid dose and control the SLE activity, we initiated combined therapy with an immunosuppressive drug. One patient who presented with AIHA, joint symptoms, and thyroiditis was initially administered leflunomide in addition to prednisolone, and this patient developed severe drug-induced hepatitis and dermatitis. Thus, MMF was substituted. Both patients responded well and their symptoms finally resolved.



Specific immunosuppressive therapy should be monitored, and drug-induced side effects should be avoided.

In conclusion, AIHA may be common and initially present in pediatric SLE patients. However, for patients with prolonged bleeding, a further workup including LAHPS is suggested. It is a rare but life-threatening event that should be recognized and treated early.

### Author contributions

Xian-Mei Huang conceived and designed the study and provided clinical research. Yan Lu wrote the paper and reviewed and edited the manuscript. All authors read and approved the manuscript.


### Declaration of conflicting interest

The authors declare that there is no conflict of interest.

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