Autoimmune Hemolytic Anemia as the Initial Manifestation of a New-Onset Systemic Lupus Erythematosus in a Patient with Suspected Tick-Borne Disease

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Abstract

Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that can affect multiple organ systems. Hematologic manifestations are commonly identified in SLE; however, autoimmune hemolytic anemia is an uncommon hematologic complication which may result in severe illness requiring emergency intervention. We report a case of a 55-year-old male with a Coombs-mediated hemolytic anemia as the presenting manifestation of SLE. Treatment included intravenous corticosteroids followed by intravenous immunoglobulin (IVIG), which ultimately resulted in resolution of his symptoms.

Introduction

SLE is a chronic multisystem autoimmune disease that affects approximately 160,000 to 300,000 people in the United States.[1] Hematologic manifestations are common, occurring in 10-83% of adult-onset SLE cases.[2] Autoimmune hemolytic anemia, however, is an uncommon hematologic complication described in only 4% of adult-onset SLE cases.[3]

Case Report

A 55-year-old Caucasian male presented to the hospital with a maculopapular rash involving the trunk, back, bilateral upper and lower extremities as well as right thigh swelling and pain. One week prior to presentation, he reported more than 50 tick bites on his right lower extremity after walking through tall grass in a wooded area. He removed the ticks but could not determine the duration the ticks had been attached to the skin. He reported progressive swelling, redness, and pain involving his right lower extremity as well as the development of fever and chills following the tick bites. Subsequently, he developed a maculopapular rash covering his bilateral upper and lower extremities, trunk, and back. He also began to experience generalized weakness. Four days prior to admission, he was prescribed oral ciprofloxacin 500 mg twice daily by his primary care physician, but his symptoms had not improved. His past medical history was unremarkable. He reported a 90 pack-year smoking history but quit smoking 15 months previously. He worked as a farmer and industrial worker. Prior to presentation to the hospital, his only medications included aspirin, diphenhydramine as needed for itching, and ciprofloxacin. Review of systems was positive for joint pain. However, he denied any prior history of photosensitivity, mucosal ulcerations, seizures, serositis, Raynaud syndrome, sicca symptoms, alopecia, or hypercoagulability. Physical exam revealed abnormal findings of tachycardia with a heart rate of

105 beats per minute and the aforementioned rash. The remainder of the physical examination was unremarkable.

Upon admission to the hospital tick-borne illness serologies were ordered. He was started on empiric doxycycline 100 mg oral twice daily for suspected tick-borne illness. Initial laboratory evaluation revealed white blood cell count 13.5 x 109/L (4-12 x 109/L), hemoglobin 12.2 g/dL (12.1-17 g/dL), hematocrit 35.9% (36-49%), platelet count 138 x 109/L (130-400 109/L), total bilirubin 6.4 mg/dL (0.0-1.5 mg/dL), direct bilirubin 1.8 mg/dL (0.0-0.3 mg/dL), alanine aminotransferase 30 IU/L (0-50 IU/L), aspartate aminotransferase 16 U/L (0-45 U/L), and alkaline phosphatase 71 U/L (28-136 U/L).

On the third day of hospitalization, he was found to have worsening leukocytosis and anemia with white blood cell count of 40.2 x 109/L and hemoglobin of 5.5 g/dL. His total bilirubin had increased to 12.6 mg/dL. Additional labs were drawn, including lactate dehydrogenase of 1342 U/L (100-350 U/L), haptoglobin less than 30 mg/dL (37-184 mg/dL), and a positive Coombs test with spherocytes noted on peripheral blood smear. Immunologic studies were ordered including an anti-nuclear antibody (ANA), IgA, IgM, and IgG levels. Additionally, two units of packed red blood cells were administered. Infectious disease and hematology consultations were obtained.

The patientâ€™s rash improved with continuation of doxycycline 100 mg by mouth twice daily. Blood cultures remained negative throughout his hospitalization. He was started on IV methylprednisolone 125 mg daily and folic acid 5 mg oral daily on the fourth day of hospitalization. Despite transfusion and corticosteroid therapy, his hemoglobin remained very low at 5.2 g/dL and his total bilirubin continued to rise to 12.6 mg/dL. Therefore, a three day course of IV immune Globulin (IVIG) 1000mg/kg daily was initiated.

ANA was found to be positive with a titer of 1:320 (less than 1:80) in a homogenous pattern. Double stranded-DNA antibody (dsDNA) and anti-histone antibody were both positive. Serologies for acute tick-borne diseases including ehrlichiosis, Lyme disease, tularemia, and Rickettsia were negative.

Following the course of IVIG therapy, continuation of IV corticosteroids, and an additional three units of packed red blood cells, his hemoglobin stabilized at 8.3 g/dL and his weakness improved. He was discharged after ten days with a 30 day oral corticosteroid taper and instructions to continue doxycycline 100 mg by mouth twice daily for a total of 28 days.

Discussion

The diagnosis of SLE is often very complicated and is based on the presence of a combination of symptoms and immunologic laboratory findings. Criteria to aid in the diagnosis of SLE have been developed primarily for research purposes. The American College of Rheumatology criteria for a diagnosis of SLE requires four of the following[5]:

1. Malar Rash
2. Discoid Rash
3. Photosensitivity

4. Oral Ulcers
6. Pleuritis or Pericarditis
7. Renal Disease- Cellular casts or persistent proteinuria (>0.5g/day or >3+)
8. Neurologic Disorder- Seizures or Psychosis (not attributed to another cause)
9. Hematologic Disorder- Hemolytic anemia (any occurrence) or Leukopenia (less than 4,000/mm3), Lymphopenia (less than 1,500/mm3), or Thrombocytopenia (less than 100,000) on at least 2 occasions
10. Immunologic Disorder- anti-dsDNA antibody, anti-Smith, positive antiphospholipid antibodies (including anticardiolipin IgM and IgG antibodies as well as lupus anticoagulant)
11. Positive Antinuclear Antibody

Hematologic manifestations are common, occurring in 10-83% of adult-onset SLE cases.[3] Autoimmune hemolytic anemia (AIHA), however, is an uncommon hematologic complication described in only 4% of adult-onset SLE cases.[3] AIHA most commonly presents at the time of diagnosis or prior to the diagnosis. Up to two-thirds of patients with SLE develop the first occurrence of hemolytic anemia at the onset of the disease. AIHA in patients with SLE has been shown to have an association with anticardiolipin IgG and IgM antibodies, anti-double stranded DNA antibodies, and the presence of a lupus anticoagulant.[6] Patients with AIHA and anti-dsDNA antibodies exhibit an increased risk of severe complications of SLE including renal disease, central nervous system disorders, thrombosis, and serositis.[7] A study published in Lupus in 2008 found SLE patients with AIHA had a 25% increase in proteinuria, 17% increase in cellular casts, 13% increase in seizures, as well as statistically significant differences in rates of serositis and other hematologic disorders. This study also demonstrated that an absence of thrombocytopenia in patients with SLE and AIHA, which was exhibited by the patient in this case, carries an increased association with the presence of anti-dsDNA antibodies.[8] The presence of anti-dsDNA antibodies is associated with an increased risk of renal disease. Additionally, AIHA independent of the presence of anti-dsDNA antibodies has also been associated with an increased risk of renal disease.[8]

There is controversy with regard to the pathophysiology of subset and role of anticardiolipin antibodies in AIHA. Some studies suggest an association with IgM anticardiolipin antibodies, while other studies have shown anticardiolipin antibodies exhibiting anti-red blood cellRBC effectstibodies in SLE patients with AIHA. In patients with SLE, AIHA is typically associated with, IgG autoantibodies of the IgG type are associated with AIHA rather than cold autoantibodies, which are typically IgM autoantibiodies.[7,9] IgG Warm antibodies account for 65-70% of AIHA in the general population.[10]

Hallmark findings of AIHA include an elevated reticulocyte index, presence of spherocytes, elevated LDH, elevated total and indirect bilirubin and low haptoglobin. Diagnosis can be further suggested by a positive direct antiglobulin test (Coombs), which signifies binding to the erythrocyte by IgG, C3b, or both.[10]

The disease may progress rapidly and requires prompt diagnosis and treatment to ensure improved patient morbidity and mortality. The disease may progress rapidly and requires prompt diagnosis and treatment to ensure improved patient morbidity and mortality. Glucocorticoids are recommended as the first-line agent for therapy and are effective in 50-90% of cases. AIHA will

resolve in approximately 20% of patients with initial corticosteroid therapy alone, while 50-60% of patients will require maintenance doses of corticosteroids and 20-30% of patients will require additional therapies.[11] Second-line agents include splenectomy, IVIG and immunosuppressive medications, including rituximab. Splenectomy remains the preferred second-line option, however, there are no prospective, randomized data to guide clinical decision making regarding any of the therapeutic options.[11] In this case, the patient did not respond to initial IV corticosteroid therapy, but had resolution his symptoms with IVIG. There is a need for further study to be done evaluating the efficacy of second line therapies in patients who do not respond to IV corticosteroids

References

1. Helmick CG, Felson DT, Lawrence RC, et al. Estimates of the prevalence of arthritis and other rheumatic conditions in the United States: Part I. Arthritis Rheum. 2008;58(1):15â€“25.

2. Fayyaz A, Igoe A, Kurien BT, et al. Haematological manifestations of lupus. Lupus Science & Medicine. 2015 Mar;2(1).

3. Gormezano NWS, Kern D, Pereira OL, et al. Autoimmune hemolytic anemia in systemic lupus erythematosus at diagnosis: differences between pediatric and adult patients. Lupus. 2017;26(4):426â€“430.

4. Hochberg MC. Updating the American college of rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis & Rheumatism. 1997;40(9):1725.

6. Skare T, Damin R, Hofius R. Prevalence of the American College of Rheumatology hematological classification criteria and associations with serological and clinical variables in 460 systemic lupus erythematosus patients. Brazilian Journal of Hematology and Hemotherapy. 2015 Jan31;37(2):115â€“119.

7. Kokori SI, Ioannidis JP, Voulgarelis M, et al. Autoimmune hemolytic anemia in patients with systemic lupus erythematosus. The American Journal of Medicine. 2000;108(3):198â€“204.

8. Jeffries M, Hamadeh F, Aberle T, et al. Haemolytic anaemia in a multi-ethnic cohort of lupus patients: a clinical and serological perspective. Lupus. 2008;17(8):739â€“743.

9. Sultan SM. Prevalence, patterns of disease and outcome in patients with systemic lupus erythematosus who develop severe haematological problems. Rheumatology. 2003 Jan;42(2):230â€“234

10. Liebman HA, Weitz IC. Autoimmune Hemolytic Anemia. Medical Clinics of North America. 2017;101(2):351â€“9.

11. Zanella A, Barcellini W. Treatment of autoimmune hemolytic anemias. Haematologica. 2014;99(10):1547â€“1554.