

An unusual association between anti-histone antibody seropositive SLE, autoimmune hemolytic anemia, and herpetic rash: A case report

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ABSTRACT

Systemic lupus erythematosus (SLE) is an autoimmune disease associated with several autoantibodies targeted to nuclear and cytoplasmic antigens. Positivity of the serum antinuclear antibody (ANA), double stranded (ds) DNA, anti-smith (sm) antibody are essential for the diagnosis of SLE. Anti-histone antibody is usually present in drug-induced SLE. Autoimmune hemolytic anemia (AIHA) in SLE is usually mediated by warm IgG anti-erythrocyte antibodies. Our case evaluation revealed negative anti-ds antibody and anti-smith antibody, low C3 and C4 complement level, strong anti-histone antibody-positive status, and AIHA. She responded with intravenous methyl prednisolone and showed significant clinical improvement. Anti-histone antibody-positive SLE presenting with AIHA is rare, probably we are reporting the first case.

Keywords: Anti-histone antibody, antinuclear antibody, autoimmune hemolytic anemia, complement level, lymphoproliferative disorder

Introduction

Systemic lupus erythematosus (SLE) is an autoimmune disease in which organs and cells undergo damage initially mediated by tissue binding autoantibodies and immune complexes.^[1] For the diagnosis of SLE, revised criteria of the American College of Rheumatology (ACR)^[2] are essential. Diagnosis of SLE can be made when antinuclear antibody (ANA) is present along with anti-double-stranded (ds) DNA and or anti-smith (sm) antibodies.^[3] Sometimes only ANA can be positive in SLE.^[2] Hematological abnormalities are usually present in SLE. It includes anemia, thrombocytopenia, and leucopenia. Anemia in SLE is usually manifest as anemia of chronic disease, which occurs in 50% of the cases.^[2] (in our case the hemoglobin was

down to 3.7 g). Autoimmune hemolytic anemia (AIHA) which was also present in our case usually occurs in 10% of the cases.^[2] Usually warm-IgG type antibody-related AIHA occurs in SLE.^[2] We report a rare case of AIHA with anti-histone antibody-positive SLE [Figure 1]. Anti-histone antibody has less female predilection than SLE. They are common in drug-induced lupus. However, they are seen in chronic infection. The most frequently used drugs responsible for anti-histone antibody-positive SLE include Hydralazine, Procainamide, Isoniazid, Methyldopa, Quinidine, Minocycline, Chlorpromazine, inhibitors of interferons, and tumor necrosis factor. There was an approximate 70% positive rate of anti-histones antibodies in SLE patients.^[1]

Case Study

A young lady presented with shortness of breath, generalized weakness, and joint pain for a week. She also had a complaint of upper abdominal pain. She was a diagnosed case of hypothyroidism,

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dyslipidemia, and obesity. Her family history was not relevant. She was febrile (temperature 100°F), icteric, and severely pale. Her blood pressure was 110/76 mm Hg, pulse 118/min regular, respiratory rate 22/min, and SpO₂ 99% on ambient air. Her respiratory and cardiovascular system examinations did not reveal any abnormalities. Her abdominal system examination revealed mild splenomegaly (15 cm). During hospital stay, she developed a herpetic rash for which she was put on Acyclovir therapy [Figure 2]. She responded to the therapy and became asymptomatic after two weeks [Figure 3]. Herpes Zoster infections occur at an increased frequency among patients with SLE compared to the general population and carry significant morbidity. Patients who have had severe manifestations of Lupus are at greatest risk of Zoster, though not necessarily at the time of disease flare or immunosuppressive therapy. If disease activity allows, a reduction in Prednisone dosage may reduce the risk of bacterial superinfection during Zoster episodes. Her blood investigations revealed normal total leukocyte count (8000/UL), indirect bilirubin (0.71 mg), direct bilirubin (1.35 mg), reticulocyte count (9%), ESR-80, CRP-1.39, dengue NS1 antigen-negative, TPO-Ab-20, lactate dehydrogenase (LDH) (648.6), direct Coomb's test strongly positive. Her hemoglobin electrophoresis shows: HbA: 95.6% HbF: 1.6% HbA2: 2.8%. Her prothrombin time and INR were normal. Her ECG showed sinus tachycardia. Stool for occult blood was negative. CECT scan of abdomen revealed splenomegaly. Her blood culture was found to be sterile twice. Viral hepatitis profile, tuberculosis, and HIV I and II were negative. She had a positive ANA and anti-histone antibody, but negative anti-double-stranded DNA (anti-dsDNA), and anti-smith-antibody (sm). Complements C3 and C4 were low. So the differential diagnosis included autoimmune hemolytic anemia, bacterial or viral infections, and lymphoproliferative disorders. She was put on high dose of steroids and packed red blood cell transfusions were given. Treatment with high dose of intravenous methylprednisolone proved effective gradually. Her symptomatic anemia was corrected by further packed cell transfusion. She became asymptomatic and was discharged on oral Prednisolone, Thyroxine, Pantoprazole, and Calcium. Three weeks after discharge, her hemoglobin level reached to 12.5 g.

Discussion

Patients with SLE may have positive ANA with negative anti-ds DNA and anti-sm-antibody or positive anti-ds DNA and anti-sm-antibody. So, for the diagnosis of SLE, positive antibody test is more important than negative antibody test, as in our case, ANA and anti-histone antibody turned out to be positive but anti-ds DNA and anti-sm antibody turned out to be negative. Negativity or positivity of the test is also dependent on lab condition and reporting facilities. High index of clinical suspicion is essential for the diagnosis of such type of disease. Our patient had arthritis, hemolytic anemia, positive ANA, and anti-histone antibody, which included 4 out of 11 revised ACR criteria for SLE diagnosis. Positive ANA is not specific for SLE but has only a predictive value of 57% for Lupus.^[4,5] The presence of anti-ds-DNA and/or anti-Sm antibody is more specific for SLE.^[6] Anti-histone antibody usually present in drug-induced

Test Name	Results	Units	Bio. Ref. Interval
HISTONE ANTIBODIES, SERUM (EIA)	2.66	Units	<1.00
Interpretation			
RESULT IN UNITS	REMARKS		
< 1.0	Negative		
1.0-1.5	Weak Positive		
1.6-2.5	Moderate Positive		
>2.5	Strong Positive		
Comments			
Histone antibodies are of clinical importance in the diagnosis of drug induced Lupus erythematosus. Usually cardiac arrhythmic patients on Procainamide develop Anti Histone antibodies of which asymptomatic patients develop IgM antibodies whereas symptomatic patients develop a unique type of IgG antibodies. Histone antibodies have also been found in patients with Rheumatoid arthritis, Mixed connective tissue diseases and Progressive scleroderma.			
Sm (SMITH), ANTIBODY, IgG, SERUM (EIA)	6.80	Units	<20.00
Interpretation			
RESULT IN UNITS	REMARKS		
<20	Negative		
20-39	Weak Positive		
40-80	Moderate Positive		
>80	Strong Positive		

Figure 1: Strongly positive anti histone antibody serum level



Figure 2: Herpetic rash on face

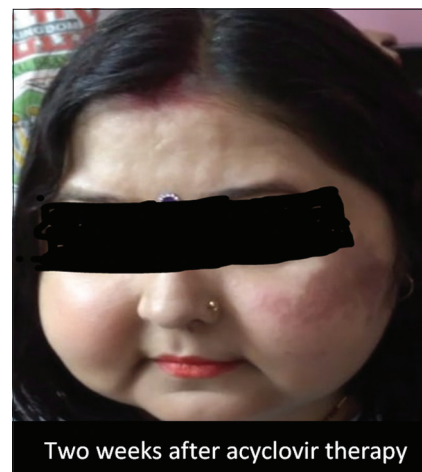


Figure 3: Two weeks after Acyclovir therapy

SLE but can also be present in rheumatoid arthritis, progressive systemic sclerosis, and mixed connective tissue disease.^[1]

Conclusion

Anti-histone antibody-positive SLE is an example of immune suppression state where superadded infection could play a role in

worsening the course. In this case, this was herpes zoster, which fortunately heals with treatment. Very few cases of AIHA in anti-histone antibody-positive SLE have been reported in the literature so far. Negative ds DNA and anti-sm antibody with positive anti-histone antibody of the patient in AIHA is rare. To the best of our knowledge, this is perhaps the first report in the literature.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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