Case Report

A Rare Combination of Autoimmune Hemolytic Anemia and Primary Antiphospholipid Syndrome Evolving into Systemic Lupus Erythematosus

Swarupa Nikhil Bhagwat, Jayashree Harihara Sharma, Dnyaneshwar Shridharrao Patale

From the Department of Transfusion Medicine, Seth GS Medical College and KEM Hospital, Mumbai, Maharashtra, India

ABSTRACT

The association of autoimmune hemolytic anemia (AIHA) with primary antiphospholipid antibody syndrome (primary APS) has not been well established. However, the occurrence of AIHA in primary APS may define a subgroup of patients with a significant risk for subsequent development of SLE. We report a case of 28 year old male who presented with clinical features of cerebral arterial thrombosis and symptomatic anemia. Subsequently the diagnosis of primary APS and warm type AIHA was made. Patient was treated for cerebral thrombosis along with glucocorticoids and least incompatible red cell concentrates. After a regular follow up of 20 months, the patient developed positivity for antinuclear antibody and oral mucosal ulcers confirming the diagnosis of SLE. This case emphasizes that patients with primary APS should always be evaluated for AIHA as this combination is not impossible, though rare. It poses a significant risk of development of SLE. Transfusion medicine specialist has a role to play in the diagnosis and management of AIHA.

KEY WORDS: *Antiphospholipid antibody syndrome, autoimmune hemolytic anemia, systemic lupus erythematosus*

Received: April, 2016.
Accepted: June, 2016.

INTRODUCTION

Autoimmune hemolytic anemia (AIHA) in the context of primary antiphospholipid syndrome (primary APS) is a rare occurrence.[1] The coexistence of AIHA and APS may define a subgroup of patients with a significant risk of subsequent development of systemic lupus erythematosus (SLE).[2] We report a case of primary APS associated with warm AIHA that subsequently developed SLE.

CASE REPORT

A 28-year-old male presented with generalized fatigue and breathlessness of 1-month duration along with right-sided weakness and difficulty in talking for 3 days. There was no history of fever, trauma, convulsions, or psychotic behavior. There was no history of significant past illness. Physical examination revealed pallor, icterus, facial asymmetry, and reduced power in the right upper and lower limbs. Mild splenomegaly (2 cm below the costal margin) was present. There was no evidence of cutaneous rash, oral ulcers, joint swellings, or tenderness at the time of presentation.

INVESTIGATIONS

Magnetic resonance imaging (MRI) of the brain showed multiple acute infarcts in the left frontoparietal region, the largest being 1.5 cm in size. MRI angiogram confirmed the thrombotic involvement of the left middle cerebral artery region. Electrocardiogram was normal. The two-dimensional echo showed no evidence of intracardiac thrombi or vegetations. However, there was mild cardiomegaly. Laboratory investigations showed hemoglobin of 6.8 g%, hematocrit 20%, total leukocyte count 8600/mm^3, neutrophils 68%, lymphocytes 32%, and platelet count of 180,000/cmm. Erythrocyte sedimentation rate was 18 mm at the end of 1 h. The peripheral smear showed hypochromasia, poikilocytosis, polychromasia, and an occasional normoblast. Corrected reticulocyte count was 2.4%. Urine examination showed the presence of trace albuminuria. Microscopic examination of the urine was normal. Serum creatinine was 1.1 mg/dL. Lactate dehydrogenase enzyme level was 540 IU/L (normal 105–333 IU/L). Serum total and indirect bilirubin were raised (6.5 mg/dL and 4.1 mg/dL, respectively). Other tests of liver function and lipid profile tests were within normal limits. Hemoglobin electrophoresis did not show any evidence of qualitative or quantitative abnormality of hemoglobin. A test for lupus anticoagulant and an assay of anticardiolipin (aCL) antibody were performed in view of cerebral arterial thrombosis. Activated partial thromboplastin time (aPTT)-lupus sensitive was prolonged to 62.6 s, while aPTT using lupus insensitive reagent was 28 s (ratio of lupus sensitive: Lupus insensitive aPTT more than 2:1). The aCL antibody levels were raised; aCL immunoglobulin M (IgM) 37.5 MPL/ml (≤12 MPL/ml - negative, 13–20 MPL/ml -

Address for correspondence:
Dr. Swarupa Nikhil Bhagwat, E-mail: swarupabhagwat@kem.edu

Access this article online

Quick Response Code:

Website: www.gjtmonline.com

DOI: 10.4103/2455-8893.189845

How to cite this article: Bhagwat SN, Sharma JH, Patale DS. A rare combination of autoimmune hemolytic anemia and primary antiphospholipid syndrome evolving into systemic lupus erythematosus. Glob J Transfus Med 2016;1:88-90.

intermediate and >80 MPL is considered high positive). aCL IgG was 159.5 GPL/ml (<14 GPL/ml indicates negative and >80 GPL/ml indicates high positive). Protein C and Protein S levels were within normal range. Antinuclear antibody (ANA), anti-dsDNA, and anti-Sm antibodies were negative. Based on the Revised Sapporo Investigational Criteria,[3] the diagnosis of APS (primary) leading to cerebral arterial thrombosis was made.

Blood bank investigations

A blood sample was received in the Department of Transfusion Medicine for blood grouping and crossmatching in view of symptomatic anemia. Moreover, the clinical and laboratory parameters indicated the presence of hemolysis. The blood group was B Rh positive. There was no difficulty in the interpretation of forward and reverse grouping except that reverse grouping showed 3+ agglutination with O Rh positive pooled red cells at 37°C. Direct antiglobulin test (DAT) with polyspecific reagent was positive (Grade 4+). Indirect antiglobulin test (IAT) was positive (Grade 3+). Both DAT and IAT were performed by column agglutination technique. Manual DAT was further performed using anti-IgG and anti-C3d monospecific antiglobulin reagents separately to characterize the protein coating the red cells. DAT was positive with anti-IgG reagent and negative with an anti-C3d reagent indicating the presence of IgG on the red cell surface. DAT positive red cells of the patient were subjected to heat elution to remove the bound IgG antibody. Autologous control, tested using the antibody-free red cells (by heat elution) and serum of the patient, was positive. The major crossmatch performed in IAT phase was incompatible with 15 B Rh positive donor units. The grade of agglutination was 3+ to 4+. The patient had no history of recent or past blood or blood component transfusion. There was no history of treatment with intravenous Igs or any medications known to be associated with immune hemolysis. The diagnosis of warm AIHA in a case of primary APS was made.

Treatment and follow-up

The patient received four units of least incompatible B Rh-positive red cell concentrate by performing titer crossmatch and comparing with autocontrol over a period of 14 days of his hospital stay. Initially, two units of red cell concentrate were administered slowly in view of symptomatic anemia on the 3rd day of admission. The patient had exertional dyspnea and orthopnea. He also had an episode of syncope during the hospital stay. The transfusions were closely monitored and acute hemolytic transfusion reactions were ruled out. Posttransfusion hemoglobin was 7.7 g% with partial relief of symptoms of anemia. Two units of red cell concentrate were transfused on the 12th day of hospital stay since hemoglobin was 7.1 g% and the patient was symptomatic. Posttransfusion bilirubin remained in the range of 3–4.5 mg/dL. Hemoglobin level increased to 8.5 g/dL.

The patient was treated with heparin, mannitol, and aspirin for cerebral arterial thrombosis. Glucocorticoid (prednisolone) was administered in view of autoimmune etiology of primary APS and hemolytic anemia. Patient's general condition improved gradually with improving power on the right side. Later, he was treated with oral anticoagulants (warfarin) with INR monitoring. At the time of discharge after 14 days, his hemoglobin was 8.2 g/dL. The patient has been repeatedly assessed at each follow-up visit for a period of past 26 months. He developed positivity for ANA with a titer 1:640 and homogeneous pattern on indirect immunofluorescence after 20 months of follow-up. Subsequently, he developed painful oral and nasal mucosal ulcers. Based on ARA classification criteria,[4,5] the case was diagnosed as SLE. At the time of diagnosis, his hemoglobin was 7.8 g/dL and platelet count of 120,000/cmm. The patient has continued with regular follow-up for renal, cardiac, and other organ involvement in SLE.

Discussion

APS is an autoimmune disorder in which vascular thrombosis or recurrent pregnancy losses occur in patients with laboratory evidence for autoantibodies against phospholipids or phospholipid-binding protein cofactors.[6] Definite APS is considered to be present if at least one of the clinical criteria and one of the laboratory criteria are met.[3] The disorder is classified as primary if no other autoimmune condition such as SLE is concurrent and as secondary if it is associated with SLE or lupus-like disease. The APS in the present case did not fulfill the diagnostic criteria for SLE at the time of presentation and first diagnosis,[4] hence was classified as primary. However, patients with primary APS are known to progress to SLE or lupus-like disease during their clinical course[7,8] as was the progression that occurred in the present case.

AIHA is characterized by shortened red cell survival and presence of autoantibodies directed against self-antigens on red cells.[9] The present case was diagnosed as warm type of AIHA based on clinical features, peripheral smear, raised bilirubin and lactic dehydrogenase along with positive anti-IgG DAT, positive autocontrol, and antibodies reacting at 37°C. Primary AIHA is idiopathic. Although an underlying autoimmune disease is one of the conditions associated with secondary AIHA, association of AIHA with primary APS has not been well established.[2] AIHA as a manifestation of primary APS has been reported with a frequency of 4%.[10] There is a highly significant association between AIHA and cardiac valvular vegetations and thickening, arterial thrombosis and livedo reticularis, epilepsy or chorea, and thus the risk of subsequent development of SLE. The combination of AIHA with primary APS in the present case also suggests the risk of developing subsequent SLE. Hence, the primary APS patients with AIHA are at risk of developing these manifestations and should be investigated for them. In another study, hemolytic anemia and Coombs positivity conferred a significant risk for subsequent development of SLE.[7] This recognition is important since SLE, being a multisystem disease with possible renal involvement, requires regular follow-up and aggressive treatment modality different from APS.[11]

The median disease duration has been reported to be 8.2 years (range: 1–14 years) for primary APS to develop into SLE or lupus-like disease.[7,8] The patient in the present case developed features of SLE after 20 months of follow-up.

The patient was initially treated with glucocorticoids in view of autoimmune etiology of APLA and hemolytic anemia. Though glucocorticoids are the first-line therapy for AIHA, transfusions are often required to temporize the patient until the glucocorticoids have had time to work.[12] Moreover, red cell transfusions often need to be administered if there are significant symptoms of anemia as was observed in the present case.[12,13]

Conclusion

AIHA, being a life-threatening disease, should be diagnosed and treated promptly where the transfusion medicine specialist has an important role to play. In addition, patients with primary APS should always be evaluated for AIHA as this combination is not impossible, though rare and poses a significant risk of development of SLE.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

References

1. Uthman I, Godeau B, Taher A, Khamashta M. The hematologic manifestations of the antiphospholipid syndrome. Blood Rev 2008;22:187-94.
2. Rottem M, Krause I, Fraser A, Stojanovich L, Rovensky J, Shoenfeld Y. Autoimmune hemolytic anaemia in the antiphospholipid syndrome. Lupus 2006;15:473-7.
3. Wilson WA, Gharavi AE, Koike T, Lockshin MD, Branch DW, Piette JC, *et al.* International consensus statement on preliminary classification criteria for definite antiphospholipid syndrome: Report of an international workshop. Arthritis Rheum 1999;42:1309-11.
4. Tan EM, Cohen AS, Fries JF, Masi AT, McShane DJ, Rothfield NF, *et al.* The 1982 revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1982;25:1271-7.
5. Hochberg MC. Updating the American College of Rheumatology revised criteria for the classification of systemic lupus erythematosus. Arthritis Rheum 1997;40:1725.
6. Rand JH, Senzel L. The antiphospholipid syndrome. In: Lichtman MA, editor. Williams Hematology. 7th ed. New York: McGraw-Hill; 2006. p. 2009-29.
7. Gómez-Puerta JA, Martín H, Amigo MC, Aguirre MA, Camps MT, Cuadrado MJ, *et al.* Long-term follow-up in 128 patients with primary antiphospholipid syndrome: Do they develop lupus? Medicine (Baltimore) 2005;84:225-30.
8. Derksen RH, Gmelig-Meijling FH, de Groot PG. Primary antiphospholipid syndrome evolving into systemic lupus erythematosus. Lupus 1996;5:77-80.
9. Packman CH. Hemolytic anemia resulting from immune injury. In: Lichtman MA, editor. Williams Hematology. 7th ed. New York: McGraw-Hill; 2006. p. 729-43.
10. Asherson RA, Khamashta MA, Ordi-Ros J, Derksen RH, Machin SJ, Barquinero J, *et al.* The "primary" antiphospholipid syndrome: Major clinical and serological features. Medicine (Baltimore) 1989;68:366-74.
11. Hahn BH. Systemic lupus erythematosus. In: Fauci AS, editor. Harrison's Principles of Internal Medicine. 17th ed. New York: McGraw-Hill; 2008. p. 2075-83.
12. Friedberg RC, Johari VP. Autoimmune hemolytic anemia. In: Greer JP, editor. Wintrobe's Clinical Hematology. 12th ed. Philadelphia: Lippincott Williams & Wilkins; 2009. p. 956-77.
13. Petz LD. A physician's guide to transfusion in autoimmune haemolytic anaemia. Br J Haematol 2004;124:712-6.