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Late Presentation of SLE and Secondary Anti-phospholipid Syndrome, Following Initial Evans Syndrome

Geetha Wickrematilake*

Department of Rheumatology, District General Hospital, Nuwara Eliya, Sri Lanka
*Corresponding author: gayaniw75@yahoo.com

Abstract **Background:** Evans syndrome associated with secondary anti-phospholipid syndrome has not been reported in case studies and we report a case of SLE and secondary anti-phospholipid syndrome diagnosed seven years after the initial diagnosis of Evans syndrome. **Case presentation:** A 21-years-old female was diagnosed with Evans syndrome since the age of 14 years, and was on treatment for seven years. At the onset of disease her immunological screening for ANA, Ds-DNA were negative. She was treated with immunosuppressants and steroids and the disease was complicated with Cryptococcal meningitis. Seven years later at the age of 21 years she started to have joint arthritis, and the ANA test converted to positive together with a positive Ds-DNA. Later on she had a single episode of unprovoked deep vein thrombosis in a leg (below knee), and became positive for lupus anticoagulant and IgM anticardiolipin antibodies. Her cardiac imaging (Echo-cardiogram) revealed that she had developed moderate pulmonary hypertension. She was treated with physiotherapy, Methotrexate, Hydroxychloroquine, Warfarin and Sildenafil with good control of the disease. Her lupus is in remission with treatment with no anaemia. **Conclusion**: Haematological manifestations of systemic lupus erythematosus could vary. Hence, Lupus should be kept in mind always during management of complicated hematological conditions as the patient might fulfill cumulative SLE classification criteria over time.

Keywords: *systemic lupus erythematosus, anti-phospholipid syndrome, Evans syndrome, anti-nuclear antibody, haemolytic anaemia*

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1. Introduction

Evans syndrome (ES) is a rare hematological disease characterized by the simultaneous or sequential occurrence of autoimmune hemolytic anemia (AIHA) and immune thrombocytopenia (ITP) [1]. A significant number of patients also have neutropenia [2]. This syndrome can be classified as primary when there is no associated disease and secondary when it is associated with other autoimmune diseases such as systemic lupus erythematosus (SLE), primary anti-phospholipid syndrome, Sjögren syndrome, IgA deficiency, Hodgkin's disease and chronic lymphocytic leukemia [3].

Studies have showed that ES seems to be a rare manifestation in SLE and 3% to 15% ES patients would develop SLE during the follow-up [4]. The median interval between presentation of ES and the diagnosis of SLE was 37 months (range 1-76) [5]. However, AIHA appeared simultaneously at the beginning of SLE in the majority [6].

We report a patient who developed SLE and secondary anti-phospholipid syndrome seven years later following the initial diagnosis of ES-showing a varied late presentation of SLE and secondary anti-phospholipid syndrome.

2. Case Report

At the age of 14 years, this patient had presented to the hospital with fever, severe anaemia (Hb=2.4g/dl), total leukocyte count 2.5 × 10 9 /L (Polymorphs-36%) and thrombocytopenia (16,000/L). She had haemolysis with elevated indirect bilirubin and LDH. The direct coombs test (DAT) was positive with cold-acting-AIHA. At that time, her anti-nuclear antibody (ANA) test and anti-phospholipid (aPL) antibody screen were negative. Her septic screen was normal. The erythrocyte sedimentation rate(ESR) by Westergren method was 98 mm /first hour. Corrected reticulocyte count was 5%.

On peripheral blood examination the smear showed marked agglutination of red blood cells, spherocytes and few nucleated red blood cells. The presence of Cold AIHA together with thrombocytopenia lead to the diagnosis of Evans syndrome(ES) and she was started on Steroids (prednisolone 1mg/kg) and immunosuppressant-Azathiprine. With this treatment, patient had frequent relapses of

haemolysis as the steroid dose was tailed off- hence had been on prednisolone doses frequently.

At the age of 17 years patient was brought back to the hospital due to an altered level of consciousness, fever and an associated neck stiffness. There were no rashes and this was not accompanied by hemolysis. Her brain CT scan was normal with positive CSF analysis for Cryptococcal meningitis. The HIV screening was negative. Patient was treated with amphotericin B and Flucytosine therapy for 2 weeks followed by fluconazole for 10 weeks with good recovery.

Later on her prednisolone dose was stopped due to good control of the Evans picture and was put on Azathioprine only. At this point her Echo-cardiogram was normal with good ejection fraction. Patient was only managed with Azathioprine for four years until she presented with an unprovoked episode of below knee DVT, episodes of arthritis and shortness of breath on exertion. However, ANA had become positive by this time with coarse speckled pattern at a ratio of ≥1/320, with positive DsDNA levels (150 IU/mL, normal range 35-55 IU/mL).

With history of hemolytic anaemia, arthritis, and with positive immunology screen she was diagnosed as a patient with SLE. Her rheumatoid factor was positive (64iu/l-normal <8iu/l), with negative anti-cyclic citrullinated peptide (anti-CCP). The complement C4 was low 9mg/dl (20-50mg/dl) with normal C3 levels. Complement C3/C4 are often depressed in patients with active SLE as a result of consumption by immune complex–induced inflammation. Her immunoglobulins showed mild elevation in IgM fraction only (363 mg/dl, normal 47-147mg/dl) and had normal serum protein electrophoresis. Serum protein electrophoresis was arranged as this patient with ES had elevated IgM immunoglobulin and these could associate lymphomas.

Her lupus anticoagulant became positive for aPTT, DRVVT with positive anticardiolipin IgM levels- repeated twice 12 weeks apart. The repeat echocardiogram revealed moderate pulmonary hypertension. The Ro/La antibodies, chest imagine were normal.

Patient was switched on to Methotrexate, Hydroxychloroquine, warfarin and Sildenafil with good control of the SLE, and was started on Alendronate due to long term steroid use.

3. Discussion

Since the diagnosis of ES the patient had been on steroids and Azathioprine which has predisposed her to the development of Cryptococcal meningitis. The diagnosis of SLE was confirmed with history of haemolytic anaemia, arthritis, positive ANA and Ds DNA tests.

Thrombocytopenia in SLE patients can be caused by anti-phospholipid syndrome. Thrombocytopenia is evident in 30-40% of patients with anti-phospholipid syndrome [7].

Management and outcome is different in primary and secondary ES and rarely splenectomy may be required for primary Evans syndrome with persistently low platelet count, whereas this may not be necessary in autoimmune diseases like SLE. Drugs reported being used in the treatment of refractory AIHA in SLE include IVIG, Azathioprine and other immunosuppressive medications as well as Danazol and Rituximab. Rituximab therapy is safe and efficacious inducing long-term clinical remission [8].

Our patient responded well to management with methotrexate and hydroxychloroquine therapy for SLE without needing additional immunosuppression.

4. Conclusion

SLE classification criteria are cumulative over time. Hematological complications are very common in SLE. Hence, patients with hematological complications should be kept under strict surveillance as they could develop SLE even after a long time as in this patient.

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