

SUCCESSFUL USE OF INTRAVENOUS IMMUNOGLOBULIN (IVIg) FOR ANTIPHOSPHOLIPID SYNDROME (APS)-ASSOCIATED EVAN'S SYNDROME

Aileen U. Agbanlog M.D.* and Sandra V. Navarra, M.D.*

ABSTRACT

Background: Antiphospholipid syndrome (APS) is an autoimmune, pro-thrombotic disorder in the presence of circulating antiphospholipid antibodies. Evan's syndrome is defined as the presence of autoimmune hemolytic anemia and autoimmune thrombocytopenia is strongly associated with APS and presents a difficult management challenge. Although experience remains limited and uncontrolled mainly due to the prohibitive costs of the drug, the use of intravenous immunoglobulin (IVIg) – in combination with high dose steroids - may be beneficial - with reported decline in anticardiolipin antibodies - in the treatment of APS-related manifestations including Evan's syndrome, especially when anti-coagulation is contra-indicated.

Setting: St. Luke's Medical Center – a tertiary care hospital

Keywords: Antiphospholipid Syndrome, Evans' Syndrome, Intravenous immunoglobulin (IVIg)

INTRODUCTION

Antiphospholipid syndrome (APS) is a multisystem prothrombotic disorder characterized by a variety of clinical manifestations including fetal loss, thrombocytopenia, hemolytic anemia, livedo reticularis, seizures, with the presence of antiphospholipid antibodies such as anticardiolipin antibodies (aCL) and lupus anticoagulant.

Thrombocytopenia, frequently found in APS patients, has an incidence of 22-42% in different series. AIHA -defined as anemia in the presence of antibodies against RBC, evidenced by either a direct or indirect Coomb's test is a common phenomenon in autoimmune diseases, although it was only rarely described in APS.¹ In a series by Rottem *et al*, AIHA was present in 10.4% of patients with APS,¹

and was found to be significantly associated with the development of cardiac valvular vegetations, arterial thrombosis and CNS signs of epilepsy. Anticardiolipin antibodies could contribute to the pathogenesis of autoimmune haemolytic anemia acting as antierythrocyte antibodies.²

Evan's syndrome (ES), described as the combined occurrence of thrombocytopenia and autoimmune hemolytic anemia is known to have a poor prognosis. This condition generally runs a chronic course and is characterized by frequent exacerbations and remissions.³ First-line therapy is usually corticosteroids and/or intravenous immunoglobulin (IVIg), to which most patients respond; however, relapse is frequent. More recently a small number of patients have been treated with rituximab, which induces remission in the majority although such responses are often sustained for <12 months.

The occurrence of Evan's syndrome in APS is not commonly reported. There were only six published case reports/series in PUBMED database on the simultaneous occurrence of these two conditions.⁴⁻⁹

We report a case of a 50-year old female with APS and Evans syndrome successfully treated with IVIg.

Case:

The patient is a 50 year old female grade school teacher, who presented with a history of recurrent thrombosis starting at age 27, when she first developed post partum deep vein thrombosis on her left lower extremity after delivery of her first child. Her second pregnancy was terminated due to premature fetal demise at 6 months age of gestation; placental examination revealed placental infarcts. She was briefly maintained on warfarin, but this was discontinued on her third pregnancy which was prematurely delivered at 6 months age of gestation. She had a stroke at 42 years old manifesting as transient hemianopsia. Since then, warfarin 5mg tablet once a day was resumed and titrated according to INR. She also started to have recurrent seizures described as generalized tonic-clonic and sometimes

*Section of Rheumatology, St. Luke's Medical Center, Quezon City

Reprint request to: Aileen U. Agbanlog, M.D., Section of Rheumatology, St. Luke's Medical Center, Quezon City, Philippines. Tel No. 7230101 local 4725. Email: aileenagbanlog@yahoo.com

partial seizure but always with complete neurologic recovery. Repeated brain CT scans were normal, and she was maintained on oxycarbazepine. She also had recurrent severe headaches and dizziness.

Her current admission was prompted by a 3 week history of persistent left occipital headache described as dull and non-pulsating with associated nape pain and elevated blood pressure at 170/100 mmHg. There was no history of trauma or fall.

Physical examination disclosed an overweight patient who was complaining of severe headache. She was conscious, dysarthric and restless. Her blood pressure was 160/80 mmHg, heart rate 90 bpm, respiratory rate 22 cpm, and body temperature of 37.6°C. The precordium was adynamic with normal rate and regular rhythm, no palpable heaves nor thrills, and no murmurs appreciated. She had clear breath sounds. The peripheral pulses were full and equal. Neurologic examination revealed pupils 2-3mm equally reactive to light, intact cranial nerves, with no motor and sensory deficits and normal deep tendon reflexes.

Hemoglobin (Hgb) was 12.5 g/dL, hematocrit 36.1%, WBC 6,820/mm³ (N 75%, L14%), platelet count 180,000/mm³. Partial thromboplastin time (PTT) was more than 180 seconds, PT control 12.2 secs, test 52.5 secs or 14 %, INR 4.61. Antinuclear antibody (ANA) was positive at 1:320 (speckled pattern), and anti-Smith, RNP, dsDNA, RF, anti Ro, anti La, anti Scl 70 were all negative. IgG cardiolipin was positive at 110.5 GPL (N.V. <15), IgM cardiolipin positive at 18.1 MPL (N.V. 12.5), lupus anticoagulant (LAC) positive at 3.4. Cranial MRI revealed a subacute subdural hematoma involving both cerebral convexities, hence warfarin was put on hold. On the 3rd hospital day, she became dysarthric but with otherwise unremarkable neurologic examination. A repeat brain MRI showed progression of the subdural hematomas. The Hgb dropped to 9.9 g/dl from 12.5g/dl, with elevated WBC at 17,000/mm³ and a decrease in platelet count at 132,000/mm³; direct Coomb's test was positive and repeat C3 level also decreased to 52.2 from 91.5 mg/dl (N.V. >88). Two-dimensional echocardiography (2DEcho) showed good systolic and systolic function, with mild pulmonary hypertension at 38 mmHg by TR jet.

At intensive care, she had progressive decrease in hemoglobin and platelet counts, and received pulse methylprednisolone 1g/day for 3 days and intravenous immunoglobulin at 600mg/kg/ day (40g/day) for 5 consecutive days. Neurologic improvement was noted after the 2nd dose of IVIG. There were

no episodes of new thrombosis when warfarin was discontinued. Hgb and platelet counts gradually increased thereafter. PT and PTT also slowly improved with latest INR at 1.16, PTT at 55.4 seconds (N.V. <45). A repeat IgG and IgM cardiolipin still showed markedly elevated levels after IVIG at 207.2 GPL and 33.5 mpl respectively. Complement levels also slowly improved on the next few days. Methylprednisolone was slowly tapered to 16 mg daily and the patient was eventually discharged improved. A month later, she was started on tinzaparin 4,500 IU 0.45 ml once a day and steroid dose was eventually tapered. She has regular follow up as to date with sustained remission of APS associated-Evans syndrome.

DISCUSSION

Standard therapy of recurrent or life threatening thromboembolic events in patients with APS traditionally consists of lifelong anticoagulation in the absence of contraindications.¹⁰ Patients with the highest titers of IgG antiphospholipid antibodies have a relatively high risk of recurrent thrombotic events especially stroke, deep venous thrombosis and spontaneous abortion,¹¹ however, those with concomitant thrombocytopenia have an increased risk of bleeding making anticoagulation a challenge.

It is known that patients with associated Evans syndrome have very poor response rates and fatal outcome to conventional treatment.⁸ The most commonly used first-line therapy is corticosteroids and/or IVIG. In the acute setting, blood and/or platelet transfusions may also be required to alleviate symptoms although its use should be minimized.¹²

In our patient who had simultaneous occurrence of APS and ES, then complicated by warfarin-induced subdural hematoma, a new thrombotic episode is likely to occur in the background of a persistently elevated aCL, which can be additionally detrimental due to immunopathogenic mechanisms of the disease where anticoagulation may have no role. The beneficial role of IVIG has been realized over the past 2 decades in both experimental and clinical studies.¹³⁻¹⁹ In this case, IVIG was used to target the immunopathogenic mechanisms of Evans syndrome and APS and possibly prevent the occurrence of new thrombosis. However, there are still a few data to support its use in altering antibody levels. There were a few studies that reported a decline in aCL after IVIG,²⁰⁻²³ while the study of Galli¹⁴ did not observe such a decline.

Although the decline in aCL levels was not seen in this patient, prevention of further thrombosis can be attributed by the immunomodulatory actions of IVIg. Before receiving IVIg, the patient had 3 thrombotic events. After the initiation of IVIg, there was no occurrence of a new thrombotic episode despite the absence of anticoagulation. In selected patients with APS, IVIg may provide an additive or alternative therapy for recurrent thrombosis, though widespread use may be limited by expense and reduced availability. Hence in the current available therapeutic options, more data should be obtained in order to decide when to use anticoagulation, IVIg or both in the treatment of APS.

CONCLUSION

This case illustrates that IVIg in combination with high dose steroids provides a sustained benefit and may be life-saving in APS - associated Evan's syndrome, despite absence of decline in anti-cardiolipin titers.

REFERENCES

1. M Rottem: Krause Fraser Autoimmune Hemolytic Anemia in the Antiphospholipid Syndrome Lupus; 15 473, 2006
2. Lang B, Straub RH, Weber S, *et al.*: Elevated Anticardiolipin Antibodies in Autoimmune Haemolytic Anemia Irrespective of Underlying Systemic Lupus Erythematosus. Lupus; 6: 652, 1997.
3. Sokol RJ, Hewitt S, Stamps BK: Autoimmune Hemolysis: Mixed Warm and Cold Antibody Type. Acta Haematol; 69: 266, 1983.
4. Galindo M, Khamashta MA, Hughes GRV: Splenectomy for Refractory Thrombocytopenia in the Antiphospholipid Syndrome. Rheumatology; 38: 848, 1999.
5. Font J, Jimenez S, Cervera R, Garcia-Carasco M, Ramos-Cassals, M: Splenectomy for Refractory Evans' Syndrome Associated with Antiphospholipid Antibodies. Ann Rheum Dis. Nov; 59(11):920, 2000.
6. Avein T, Jazbec J, Kuhar M, Zupancic M: Evans Syndrome Associated with Antiphospholipid Antibodies. J Pediatr Hematol Oncol Sep; 25(9): 755, 2003.
7. Deleze M, Oria CV, Alarcon-Segovia D: Occurrence of Both Hemolytic Anemia and Thrombocytopenic Purpura (Evans' Syndrome) in Systemic Lupus Erythematosus. Relationship to Antiphospholipid Antibodies. J Rheumatology Apr; 15(4): 611, 1988.
8. A Ruckert, H Glimm, Case Report: Successful Treatment of Life Threatening Evan's Syndrome Due To Antiphospholipid Syndrome by Rituximab Based Regimen, A Case with Long Term Follow up Lupus, 16:757, 2008.
9. Fro...ow M, Jankowski M, Swadzba J, Musia... J: Evans Syndrome with Antiphospholipid-Protein Antibodies. Pol Merkuriusz Lek, Nov, 1:5, 344, 1996.
10. Lockshin, MD, Erkan, D: Treatment of the Antiphospholipid Syndrome. N Engl J Med; 349: 1177, 2003.
11. Levine Steven, Salowich-Palm L, Sawaya K: IgG Anticardiolipin Antibody Titer > 40 GPL and the Risk of Subsequent Thromboembolic Events and Death. A Prospective Cohort. Stroke; 28: 1660, 1997.
12. Norton, Alice: Management of Evans Syndrome British Journal of Haematology, 132, 125, 2005.
13. Caccavo D, Vaccaro F, Ferri GM, *et al.*: Anti-Idiotypes Against Antiphospholipid Antibodies are Present in Normal Polyspecific Immunoglobulin's for Therapeutic Use. J Autoimmun; 7:537, 1994.
14. Galli M, Cortelazzo S: In Vivo Efficacy of IVIg in Patients with Lupus Anticoagulant is Not Mediated by Anti-Idiotypic Mechanism. Am J Hematol: 38: 184, 1991.
15. Said PB, Martinuzzo ME, Carreras LO: Neutralization of Lupus Anticoagulant Activity by Human Immunoglobulin 'in vitro'. Nouv Rev Fr Hematol; 34:37, 1992.
16. Matsuda J, Gochi K, Kawasugi K, *et al.*: I Vitro Lupus Anticoagulant Neutralizing Activity of Intravenous Immunoglobulin. Thromb Res; 70: 109, 1993.
17. Yaniv Sherer, Yehuda Shoenfeld Intravenous Immunoglobulin for Immunomodulation of Systemic Lupus Erythematosus Autoimmunity Reviews 5 (2006) 153.
18. Yu Z, Lennon VA: Mechanism of Intravenous Immune Globulin Therapy in Antibody-Mediated Autoimmune Diseases. N Engl J Med; 340:227, 1999.
19. Lockshin MD: Antiphospholipid Antibody: Babies, Blood Clots, Biology. JAMA; 277:1549, 1997.
20. Spinnato JA, Clark AL, Pierangelli SS: Intravenous Immunoglobulin Therapy for the Antiphospholipid Syndrome in Pregnancy. Am J ObstetGynecol;172:690, 1995.
21. Hsiao GR, Wolf RE, Kimpel DL: Intravenous Immunoglobulin to Prevent Recurrent Thrombosis in Antiphospholipid Syndrome. Blood Coagul Fibrinolysis Jun; 14(4): 395, 2003.
22. Koschmieder S, Miesbach W, Fauth F: Combined Plasmapheresis and Immunosuppression As Rescue Treatment of A Patient with Catastrophic Antiphospholipid Syndrome Occurring Despite Anticoagulation: A Case Report.
23. Carreras LO, Perez GN, Martinuzzo ME, *et al.*: Partial Neutralization of A Lupus Anticoagulant by Human Immunoglobulin. Thromb Haemostasis; 64:32, 1990.