SYSTEMIC LUPUS ERYTHEMATOSUS AND EVAN'S SYNDROME IN A YOUNG ADULT FEMALE: A CASE REPORT

Bea Eunice E. Aspiras, MD[1], Allan E. Lanzon, MD, FPCP, FPRA[2], and Maribeth Mayo, MD, DPCP, FPSHBT, FPCTM[3]

Abstract. Systemic Lupus erythematosus (SLE) is a multiorgan autoimmune disease that affects 20-150 per 100,000 women. It is a mutagenic disease which causes formation of autoantibodies immune complexes that leads to inflammation in different organs leading to organ damage. We present a case of a young female who was newly diagnosed to have SLE. She presented with an elevated ANA, low C3 and elevated Anti-DS DNA. She first manifested with epistaxis and subsequently experienced the various complications of SLE such as infection, thrombosis, bleeding, ascites, etc. The initial presentation of normochromic, normocytic anemia and thrombocytopenia together with further work-ups supported another concomitant autoimmune disease, namely Evan's syndrome. Evan's syndrome is a rare manifestation of SLE, and is observed in only 2.73% of the population. In addition, the patient manifested with sudden onset of right-sided body weakness with Cranial CT scan findings of areas of focal infarction in the frontal lobe with concomitant acute intracranial hemorrhages. The evidence of both thrombosis and hemorrhage provided conflicting management strategies for this patient. The use of hydroxychloroquine, which is the cornerstone of lupus therapy, provided beneficial antithrombotic effects. A multidisciplinary approach to management and prudent choice of medications were vital in the success of treatment on such a complicated case.

Keywords: Systemic lupus erythematosus, thrombosis, hemorrhage, Evan's syndrome, case report

Introduction

Systemic Lupus erythematosus is a disease that affects 20-150 per 100,000 women. It is a multiorgan autoimmune disease that has high morbidity and mortality if left untreated. We present a case of a previously healthy young female presenting with epistaxis, oral ulcers, hematoma on the perinasal area with baseline laboratory findings of anemia and thrombocytopenia. Evan's syndrome is a rare disease characterized by simultaneous or sequential development of Autoimmune Hemolytic Anemia and Immune Thrombocytopenic Purpura. It is a rare manifestation of SLE observed in only 2.73% of the population. During the course, the patient also presented with cerebrovascular disease infarct with concomitant acute intracranial hemorrhages which provided conflicting management strategies for the case.

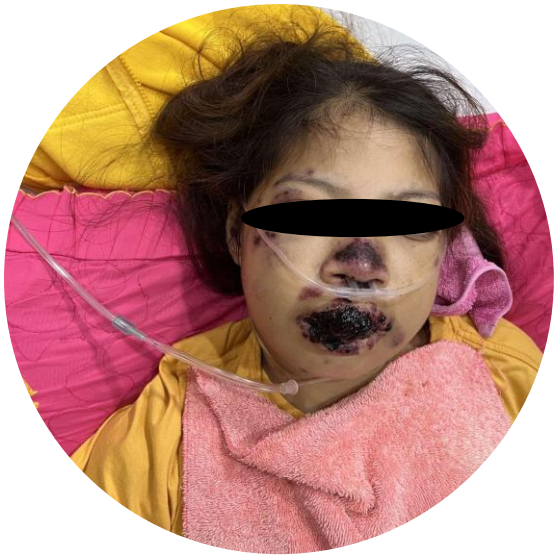
[1]Bea Eunice E. Aspiras, MD, Department of Internal Medicine, Batangas Medical Center, Philippines
[2]Corresponding authors: Allan E. Lanzon, MD, FPCP, FPRA, Maribeth Mayo, MD, DPCP, FPSHBT, FPCTM
E-mail: beaeunice.aspiras@gmail.com

Case Report

A 26 year old Filipino, female, previously healthy with no known comorbidities was admitted due to epistaxis. History started 2 weeks prior to admission when she noted multiple, flat purplish patches at the bilateral temporal and occipital areas of the head. There were no active bleeding, fever, cough, colds, body malaise noted. No consultation was done. No medications were taken.

Five days prior to admission, the patient's symptoms persisted, now associated with spontaneous bleeding of the upper and lower lips and epistaxis amounting to 2 teaspoons. This was also associated with frontal headache, 6/10 intensity, throbbing in character associated with generalized body weakness, palpitations and undocumented fever. Patient sought consultation with a private physician who prescribed Ferrous Sulfate once a day (OD), Multivitamins 1 tab OD and Paracetamol 500mg tab 1 tab q4 as needed (PRN) for

fever which provided no relief of symptoms. CBC done revealed anemia and thrombocytopenia hence the patient was advised further work-up. Persistence of symptoms prompted admission.

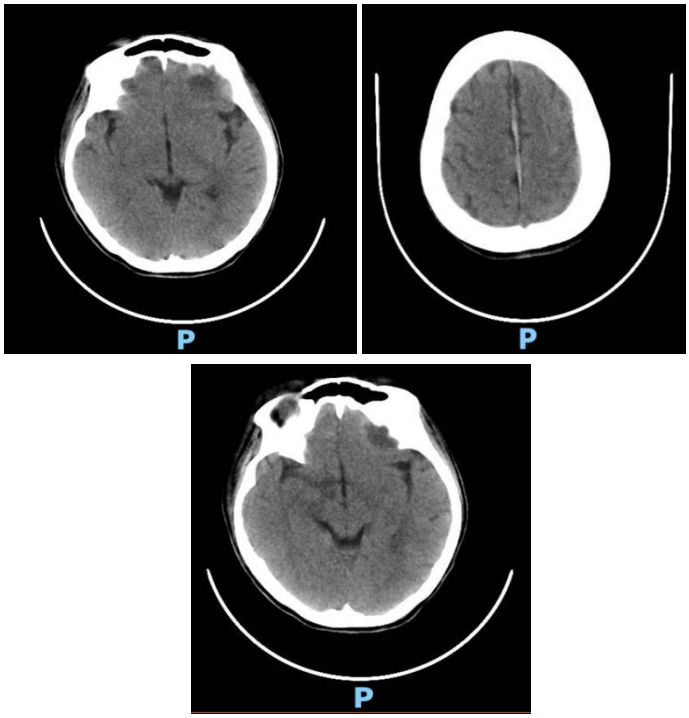


Upon admission, the patient was normotensive, tachycardic, and afebrile with normal oxygen saturation. Physical examination revealed the following pertinent findings: pallor, pale palpebral conjunctiva, violaceous discoloration on the helix of bilateral ears, hematoma on the upper and lower lips extending to the perinasal area, oral ulcers, purpuric lesions on bilateral extremities and normal neurologic exam.

On laboratory investigation, there was noted normocytic normochromic anemia, thrombocytopenia, elevated BUN, uric acid, twice elevated SGPT, 5x, SGOT elevated x 5 and hypoalbuminemia. The patient also presented with low C3, elevated ANA and antiDSDNA, positive for direct Coombs test. Peripheral blood smear revealed marked microcytosis and hypochromia with variation in size and shape and marked thrombocytopenia. Other workups such as chest Xray, thyroid function tests were normal and dengue panel was negative.

The patient was initially managed as a case of Anemia and Thrombocytopenia secondary to Blood Dyscrasia hence referral to Hematology service was done and she was transfused packed Red blood cells and platelet concentrate and Erythropoietin was started. Supplemental feeding was also started to address the malnutrition of the patient. On the 1st hospital day, the patient had a sudden onset of black tarry stools hence Omeprazole drip was started. Esophagoduodenoscopy was offered; however, relatives refused due to financial constraints. On the 4th hospital day, chest X-ray revealed progression of infiltrates hence the patient was managed as a case of Hospital Acquired Pneumonia and was started on Cefepime and Amikacin. Lupus Panel showed the following results: elevated ANA, below normal C3 and elevated Anti-DS DNA 284.54, hence the patient was managed as a case of Systemic Lupus Erythematosus, in flare and was started on the Hydroxychloroquine 200mg tab OD and Hydrocortisone 100mg IV q8. Patient was referred to Rheumatology service for co-management. The plan was to administer Methylprednisolone Pulse Therapy once the patient's infection was controlled. Furthermore, the patient was referred to ENT for evaluation and co- management of the oral ulcers and perinasal hematoma. Since the patient was not clinically responding to the started antibiotics, Cefepime was shifted to Meropenem, and Amikacin was extended for 7 more days. Mupirocin Ointment was also started for the skin lesions.

On the 10th hospital day, the patient suddenly became dyspneic, drowsy and hypotensive hence emergency intubation was done and Norepinephrine was started. Patient was then managed as a case of Acute Respiratory Failure Type 1 secondary to Hospital Acquired Pneumonia; Acute Respiratory Distress Syndrome, severe secondary to Septic Shock. There was also noted sudden onset of right-sided body weakness hence the patient was referred to Neurology service. A plain Cranial CT scan was requested which revealed areas of focal infarction at the left inferior frontal lobe and ipsilateral high parietal cortical-subcortical region with concomitant acute intracranial hemorrhages: likely, subarachnoid type in the left frontal lobe, falcine parafalcine subdural hemorrhage.



The findings of both thrombosis and hemorrhage posed conflicting management strategies for this patient. The patient was started on atorvastatin and mannitol, and hydroxychloroquine was continued. Hypernatremia was also noted and was corrected accordingly through free water feeding via nasogastric tube. Subsequently, the

patient had one episode of arrest with noted return of spontaneous circulation after 1 dose of epinephrine and chest compressions. The cardiopulmonary arrest was attributed to SLE and its multisystemic complications aggravated by sepsis. Vancomycin and Fluconazole were added for added coverage for the management of Pneumonia. Furthermore, the patient was referred to Rehabilitation Medicine for physical therapy.

Throughout the hospital stay, medications were continued and the patient was eventually weaned off ventilatory support. Bone marrow aspiration was done which yielded the following result: reactive erythroid hyperplasia with dysplastic changes in erythroid. Subsequently, the patient developed vulvar swelling with no noted fever, bleeding or discharge. The patient was referred to OB-GYNE service for co-management with noted internal examination findings: cervix closed, no cervical motion tenderness, uterus small, no adnexal mass or tenderness. Sputum CS revealed *Stenotrophomonas maltophilia* moderate growth hence antibiotics were shifted to Co-trimoxazole and Levofloxacin. On the 35th hospital day, the patient had increasing abdominal girth with positive fluid wave and grade 1-2 bipedal edema hence intravenous albumin infusion was started. Antibiotics were continued and Hydrocortisone was shifted to Prednisone 20mg/tablet, 1 tablet BID since the patient was able to tolerate oral feeding. Eventually, the patient had regression of ascites and edema with noted stable vital signs and absence of bleeding, hence she was discharged.

Upon follow-up, the patient was asymptomatic and compliant with her medications. Tapering of prednisone was done to the lowest possible dose. Her laboratories were within normal limits and she was counseled regarding family planning due to her reproductive age and possibility of high-risk pregnancy. She was also advised vaccination for influenza flu and pneumonia.

Discussion

Systemic Lupus Erythematosus is a disease that affects 20-150 per 100,000 women. It is an autoimmune disease in which tissue binding antibodies and immune complexes cause cellular and organ damage. SLE is a mutagenic disease and pathogenesis is related in large part to production of increased quantities and immunogenic forms of nucleic acids and other self-antigens, which drive autoimmune-inducing activation of innate immunity, autoantibodies, and T cells (Jameson et al, 2018). This then causes formation of autoantibodies immune complexes which causes inflammation in different organs leading to organ damage.

SLE has genetic factors such as complement and mannose-binding lectin genes and its intrinsic immunological abnormalities induced by the disease itself which predispose patients to infection. Furthermore, the various immunosuppressive treatments predispose patients to high risk of infection. Moreover, bacterial infections can release bacterial DNA associated with other bacterial molecules, complexes that can elicit autoimmunity by acting as innate stimuli of pattern recognition receptors and activating autoreactive B cells through molecular mimicry. In our patient, hospital acquired pneumonia and catheter associated urinary tract infection were managed through cultures, empiric and culture-guided antibiotics and ventilatory support.

According to the study of Pereira, et al. (1998) SLE is associated with hematologic complications including hemolytic anemia, lymphocytopenia, thrombocytopenia and neutropenia. These complications are caused by increased peripheral destruction of blood cells by circulating antibodies. In this patient, the following laboratory findings support the diagnosis of autoimmune hemolytic anemia (AIHA): anemia, increase AST, increased LDH, elevated bilirubin, increased reticulocytes, increased MCV, bone marrow aspiration findings of erythroid hyperplasia and positive direct antiglobulin test. Whereas, the following findings support the diagnosis of Immune thrombocytopenic purpura (ITP): thrombocytopenia, mucocutaneous bleeding, ecchymoses and petechiae, gastrointestinal bleeding, wet purpura and large platelet seen on peripheral blood smear.

Evan's syndrome is a rare disease characterized by simultaneous or sequential development of AIHA and ITP. It results from an alteration of the immune system that produces multiple autoantibodies targeting red blood cells and platelets. It is a rare manifestation of SLE observed in only 2.73% of the population. Majority of patients have multisystemic life threatening disease which is manifested in this case. According to case reports, Evan's syndrome in SLE responds well to corticosteroid therapy and/or intravenous immunoglobulin however there are no treatment guidelines available due to its rarity (Costallat et al, 2012).

SLE is a chronic systemic inflammatory disease that is associated with an increased risk of cerebrovascular events, which account for 10–15% of deaths in SLE (Holmqvist et al., 2015). Here, we are presented with 2 contrasting conditions which both occurred in our patient: Acute Cerebrovascular Disease Infarct and Subarachnoid Hemorrhage. The evidence of both thrombosis and hemorrhage provided conflicting management strategies for this patient.

SLE is associated with twofold increased risk of ischemic stroke. It has comorbid conditions which are also risk factors for stroke such as vasculitis, antiphospholipid syndrome and hypertension. These causes increased risk of thrombosis and immune deposits. The highest relative risk of stroke was observed at younger ages, which may be partially explained by the accelerated and premature atherosclerosis seen in SLE. It may also be due to traditional cardiovascular risk factors such as hypertension, hyperlipidemia and diabetes mellitus, which represent common comorbidities in SLE (Holmqvist et al., 2015). Systemic inflammation may also play an important role in triggering stroke as well as drug-related complications due to the

immunosuppressive therapies often used in these patients. Furthermore, other conditions that occur in SLE may contribute to the increased risk of thrombosis such as antiphospholipid syndrome, Libman Sacks endocarditis and immune deposits (e.g. autoantibody–antigen complexes, lupus anticoagulant and antiphospholipid antibodies). Strokes attributed to SLE may be explained by systemic inflammation, endothelial activation or a prothrombotic state due to antiphospholipid antibodies. Young patients with unknown cause of stroke should be screened for antinuclear antibodies (ANA) and aPL (anti-cardiolipin, anti β2-glycoprotein I and lupus anticoagulant) (Nikolopoulos et al, 2019). This patient was advised for APAS screening however was not amenable at the time due to financial constraints.

On the other hand, there is three-fold increased risk of intracerebral hemorrhage in SLE. Intracranial vasculitis and hypertension may be responsible for the increased risk of subarachnoid hemorrhage. The endothelial dysfunction seen in SLE may increase the likelihood of rupture, leading to hemorrhagic stroke (Nikolopoulos et al, 2019). Given the aforementioned mechanisms, the treatment of ischemia and hemorrhage for this patient was a balancing act. For the cerebral hemorrhage, adequate blood pressure control and initiation of mannitol for the cerebral edema were given. Whereas for the infarction, antiplatelet therapy with high-dose statins is the standard of therapy for cerebral infarction. However, due to the hemorrhages noted, aspirin cannot be administered in this case. Alternatively, hydroxychloroquine, which is the cornerstone of lupus therapy, was utilized instead for its antithrombotic effect. Although the SPARCL trial in 2006 has shown that statins increase the risk of hemorrhagic stroke, the use of statins was considered for this case. According to Endres, et al (2017), there is no significant association between statin treatment or low LDL cholesterol levels with the risk of bleeding.

SLE-related gastrointestinal involvement is clinically important, and the causes to be considered include mesenteric vasculitis, protein-losing enteropathy, intestinal pseudo-obstruction, acute pancreatitis and other rare complications such as celiac disease, inflammatory bowel diseases. For this case, it is highly likely that intestinal involvement is secondary to mesenteric vasculitis. Ascites in SLE is rarely massive; it is often painless, has a gradual onset, and is rarely reported as the first manifestation of SLE, usually following other symptoms (Ebert & Hagspiel, 2011).

Cardiovascular wise, our patient presented with hypertension with 2D echo findings of concentric left ventricular hypertrophy with adequate contractility and normal wall motion, Ejection Fraction 56%. SLE predicts increased LV mass, possibly because of inflammation-related arterial stiffening. Mechanisms by which SLE might directly induce changes in LV structure include underlying inflammatory processes leading to subclinical vasculitis, myocarditis, or vascular stiffening. Ventricular remodeling and subsequent hypertrophy may therefore result from increased inflammation-mediated vascular stiffness (Pieretti et al. 2007). SLE, in addition to traditional stimuli, augments LV mass, especially in the setting of hypertension. These findings suggest a direct disease-related effect of SLE on LV structure. LV hypertrophy is known to lead to increased risk of stroke, coronary artery disease, congestive heart failure, and sudden cardiac death in varied populations. The primary objective of treatment is the maximum long-term reduction in the risk of cardiovascular morbidity and mortality.

Conclusion

The management for complicated SLE, such as in this case, entails a multidisciplinary approach. Early recognition and individualized treatment are tantamount to the success in management. In patient's presenting with hemorrhage and thrombosis, it is a balancing act to prevent further complications. In this case, hydroxychloroquine was highly beneficial due to its ability to reduce the disease activity and its known antithrombotic effects. Further studies and case reports are needed to establish the association between Evan's syndrome and Systemic Lupus Erythematosus.

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