Case Report

SYSTEMIC LUPUS ERYTHEMATOSUS IN PREGNANCY; A RARE COMPLICATION AT FEDERAL MEDICAL CENTRE, YENAGOA: A CASE REPORT.

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Abstract

Background: Systemic lupus erythematosus (SLE) is an autoimmune, multi-systemic disease, resulting in abnormal immune response. It predominantly affects women of childbearing age. The disease may not be uncommon among black women especially Nigerians contrary to previous assumptions. A high index of suspicion is, therefore, needed especially during pregnancy in women presenting with symptoms and signs suggestive of SLE, in order to diagnose and manage this condition which can result in life-threatening complications with adverse maternal and perinatal outcomes.

Case presentation: A 32-year-old G5 $P1^{+3}$ (alive) registered for antenatal care at 8 weeks' gestation and was not known to have SLE at booking. She complained of malaise, fever, and joint pain at first contact. There was proteinuria at booking which persisted throughout her pregnancy alongside other complaints. She developed deep vein thrombosis, severe skin rashes, pre-eclampsia, eclampsia amongst other complications during the course of the pregnancy and at puerperium. Result of antinuclear antibody test was markedly elevated, anti-double stranded DNA antibody test was positive and anti-Smith antibody test was borderline. Her care was multi-disciplinary approach and she had caesarean delivery at term. The baby had neonatal lupus and late neonatal demise from complications of neonatal heart block.

Conclusion: Like a black cat in a dark night, SLE in pregnancy, a rare medical condition which we seldom encounter in our busy clinics could be missed especially in unsuspecting patients. Persistent proteinuria with skin rash should therefore raise a high index of suspicion, which should trigger a search for this life-threatening disease in pregnancy. Instituting the right management early in pregnancy with a multi-disciplinary approach will improve both maternal and foetal outcome and subsequently reduce maternal and perinatal morbidity and mortality.

Keywords: Systemic lupus erythematosus, Autoimmune, Multi-systemic disease, Life-threatening, Maternal and perinatal morbidity and mortality.

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INTRODUCTION

Systemic lupus erythematosus (SLE) is an autoimmune, multi-systemic disease affecting predominantly women of childbearing age. Pregnancy complicated by SLE is a high-risk pregnancy and as such, would require multi-disciplinary care to improve the chances of a positive pregnancy experience and a good outcome. Pregnant women with SLE could present with life threatening challenges in both the mother and her baby, which may mimic other common pregnancy complications.

CASE PRESENTATION

She is a 32-year-old booked G5 $P1^{+3}$ (alive) with last menstrual period of 22nd September, 2018 and expected date of delivery was 29th June, 2019. She

registered for antenatal care at 8 weeks of gestation. Prior to her booking, she was not known to have systemic lupus erythematosus, and as such no extra care was accorded her. However, there was a history of unusual facial rash which spontaneously resolved about 4 weeks earlier.

At booking she complained of malaise, joint pain, headache and generalized body weakness. Her chest was clear clinically, pulse was 80 beats per minutes and blood pressure 100/60 mmHg. Her abdomen was normal and her central nervous system was intact. Urinalysis revealed proteinuria of 2+, haemoglobin concentration was 12 g/dl, retroviral screening, hepatitis B surface antigen test and venereal disease research laboratory test were negative. Blood group was O 'Rh' D positive and haemoglobin genotype was 'AA'. First trimester ultrasound scan reported a singleton active intrauterine foetus at 10 weeks gestation, her expected date of delivery was 3rd July, 2019. Thick blood film for malaria parasite was positive for falciparum malaria and urine microscopy and culture done yielded no bacteria growth. She was treated for malaria and also received intramuscular tetanus toxoid and haematinics which was continued throughout pregnancy and puerperium. She was seen 4-weekly at the antenatal clinic.

At 16-week gestation, her symptoms persisted, urinalysis revealed proteinuria 2+, repeat urine microscopy, culture and sensitivity yielded no growth of bacteria and thick blood film for malaria parasite was negative. Full blood count, serum electrolyte, urea, creatinine and uric acid were normal. She was commenced on malaria prophylaxis with oral sulphadoxine/pyrimethamine (SP) 1500 mg/75 mg 4-weekly, and oral vasoprin® 75 mg daily (low-dose aspirin), which was continued until 36 weeks of pregnancy. She was given 2-weekly appointment thereafter.

At 18-week gestation, she complained of right calf swelling and pain, fever, malaise, joint pain, mild skin rashes on the upper and lower limbs [Figures 1, 2 & 3]. She was not in respiratory distress and her chest was clear. Her blood pressure was normal and the foetal heart tone was heard. There was right lower limb oedema with engorged calf veins, tenderness and differential warmth. She was admitted into the ward and was co-managed with the haematologist and nephrologist. D-dimer test result was markedly elevated = 6,886 ng/ml, (normal range <1000 ng/ml), Doppler ultrasound scan of the right calf vein confirmed deep vein thrombosis. Anomaly scan and ultrasound scan of the kidneys, ureters and bladder were normal. Full blood count revealed thrombocytopaenia ($98,000/mm^3$) and anaemia (Hb concentration of 7.6 g/dl). Serum electrolyte, urea, creatinine and uric acid were normal. Urinalysis revealed proteinuria 2+ and haematuria 1+, mid-stream urine microscopy, culture and sensitivity yielded no bacteria growth. She was commenced on subcutaneous enoxaparin (clexane®) 80 mg 12-hourly and use of compression stockings. Her clinical condition improved significantly and she was discharged home after 10 days on admission on subcutaneous clexane 40 mg daily.

She was seen at the antenatal clinic at 20, 22, 24 and 26-week gestation. Joint pain, malaise and proteinuria persisted but her blood pressure remained normal. She received the second dose of SP for intermittent preventive treatment for malaria prophylaxis according to schedule. She had uterine artery Doppler done at 24-week gestation which showed increased resistivity index.

At 28-week gestation, she was admitted and treated for malaria in pregnancy to rule out chronic kidney disease (CKD). Her haemoglobin concentration was 8 g/dl, and she received 2 units of packed cells. On admission, she developed hypertension, her blood pressure was 150/90 mmHg, proteinuria persisted. She was commenced on oral alpha methyl dopa 250 mg 8-hourly and nifedipine 20 mg 12-hourly. She also received intramuscular dexamethasone 12 mg 12-hourly for 24 hours and continued oral vasoprin® and haematinics. Her blood pressure returned to normal and she was discharged home after 1 week on admission on anti-hypertensives. Upon

discharge, she was given weekly antenatal clinic appointment and a 4-weekly growth scan was ordered.

At 34-week gestation, she developed generalized erythematous patches on her skin with scaling rashes which progressively became worse at 37-week gestation (the erythematous rashes became hyperpigmented at 37-week gestation). She complained of malaise, pain in her joints, painless oral ulcers, low-grade fever, and memory loss. The blood pressure rose to 160/100 mmHg, symphysio-fundal height was 34 cm, with a singleton foetus in longitudinal lie and cephalic presentation. The descent was 4/5. There was proteinuria of 3+, anaemia (haemoglobin concentration was 9 g/dl), leukopaenia and thrombocytopaenia. Serum electrolyte, urea, creatinine and uric acid were normal, liver function test was normal.

She was admitted for delivery and reviewed by the dermatologist, cardiologist and haematologist. Obstetric ultrasound scan with foetal biophysical profile gave a score of 4/10 with an estimated foetal weight of 2.3 kg. A diagnosis of severe pre-eclampsia with intrauterine growth restriction (IUGR) was made. She received a unit of fresh whole blood, parenteral magnesium sulphate ($MgSO_4$) by Pritchard's regimen and intravenous hydralazine for blood pressure control.

She was counselled on the diagnosis made and its line of management, and offered an urgent caesarean delivery. Consent for caesarean section was obtained and the procedure was done same day at 22:25 hours under spinal anaesthesia with the neonatologist in attendance. She was delivered of a life female baby with Apgar scores of 8 and 9 in the 1st and 5th minutes respectively, her birth weight was 2.2 kg and the placenta weighed 0.2 kg. At birth, the baby had skin rashes on the face, chest, back and thigh (neonatal cutaneous lupus erythematosus). Blood loss at surgery was 500 ml and she received 2 units of blood. She received intravenous fluid 5% dextrose-saline 1L 12-hourly for 24 hours and was also commenced on parenteral amoxicillin/clavulanic acid 1.2 g 12-hourly, metronidazole 500 mg 8-hourly, gentamycin 80 mg 8-hourly, pentazocine 30 mg 6-hourly, and suppository diclofenac 100 mg 12-hourly. She continued the maintenance dose of $MgSO_4$ 5 g 4-hourly for 24 hours and was on intravenous hydralazine for blood pressure control, during the immediate post-operative period.

A diagnosis of systemic lupus erythematosus was made at delivery. Result of antinuclear antibody test was markedly elevated, anti-double stranded DNA antibody test was positive and anti-Smith antibody test was borderline. The baby at special care baby unit (SCBU) was also noticed to have congenital heart block.

Her immediate post-operative condition was satisfactory and her 1st post-operative day was uneventful. The blood pressure ranged between 120-140/60-90 mmHg. She was continued on subcutaneous clexane® 40 mg daily, oral nifedipine 20 mg 12-hourly and lisinopril 10 mg daily. Urethral catheter was discontinued at the completion of $MgSO_4$. Her condition improved and parenteral antibiotics were converted to oral medication after 48 hours for 5 days. Oral tramadol 50 mg 8-hourly and paracetamol 1 g 8-hourly were given for analgesia. On the 6th post-operative day, she had elevated blood pressure of 160/110 mmHg and developed recurrent generalized tonic-clonic seizures. Despite recommencing $MgSO_4$ and parenteral diazepam 10 mg stat, seizure continued and she subsequently lapsed into coma.

She was immediately moved to the intensive care unit (ICU), and was placed on ventilator. There was proteinuria 3+, full blood count, serum electrolyte, urea, creatinine and uric acid, liver function test, brain computer tomographic scan, electrocardiogram, and echocardiogram were normal. She was co-managed with the anaesthetist, neurologist, haematologist, dermatologist and cardiologist. After 2 days she regained consciousness. She was discharged home on the 20th post-operative day after counselling on contraception, family planning and the need for pre-conceptional care and a specialist obstetrician-based care in her next pregnancy. She was given a-week appointment to the post-natal clinic. Her

baby was discharged from the special care baby unit after 21days.

At her 28th post-operative day, she was seen at the post-natal clinic. She had no complaint; the skin rashes had subsided and her blood pressure had returned to normal. Her antihypertensive medications were tapered and she was asked to return at 6-week post-partum. She was weaned off antihypertensives at her 6th week post-partum visit, her clinical state had improved, blood pressure was normal and the skin rashes had significantly subsided. However, her baby was reported to have died during sleep on her 28th day of life. She was re-counselled on the need for a small family size, contraception and family planning. She was referred to the family planning clinic, cytology clinic for Papanicolaou smear and to continue her care at the dermatology clinic.

She had implanon NXT inserted and continued on oral prednisolone 10 mg daily. The Papanicolaou smear was normal.

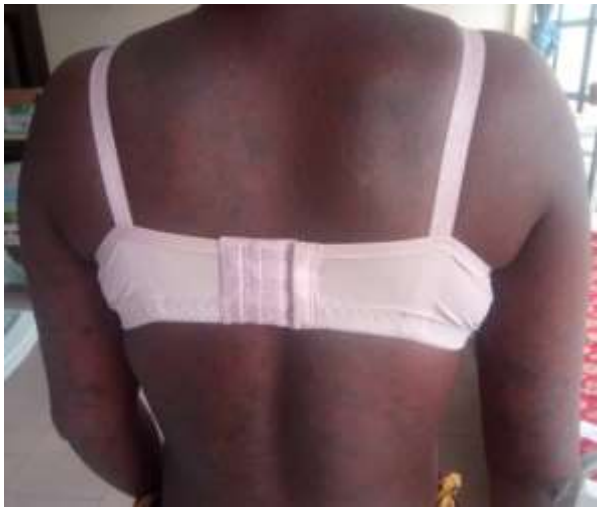

Figure 1. Hyperpigmented rashes at the back of the patient.

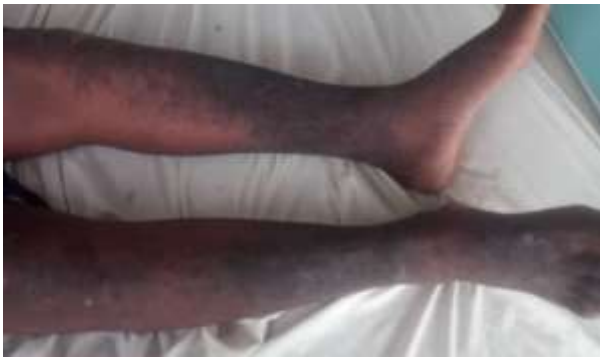

Figure 2. Hyperpigmented rashes on the legs of the patient.

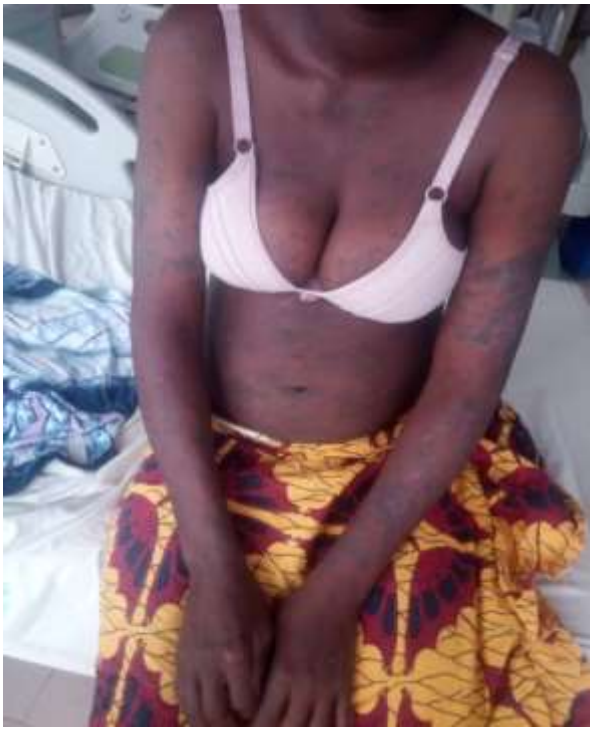

Figure 3. Hyperpigmented rashes at the upper limbs, chest and abdomen.

DISCUSSION

Systemic lupus erythematosus is a heterogenous autoimmune disease with a complex pathogenesis due to interactions between genetic and environmental factors, resulting in abnormal immune response.[1] These result in cellular and tissue damage when autoantibodies or immune complexes are produced and directed at one or more cellular nuclear components. Some of these autoantibodies produced in patients with lupus include antinuclear antibody (ANA), anti-double-stranded (ds)-DNA antibodies, anti-smith antibody (anti-sm), antiphospholipid antibodies (APS), antiplatelet antibodies amongst others.[1,3]

About 90 percent of cases of lupus occur in women, with a prevalence of 1 in 500 among women of childbearing age.[2] This may be the reason the disease is encountered relatively more frequent during pregnancy.[4,5] There is a genetic predisposition to this condition with a 10 percent frequency in patients with one affected family member.[5] The relative risk is increased if there is inheritance of the "autoimmunity gene" on

chromosome 16 that predisposes to SLE.[1] However, there was no family history in this patient.

SLE is not a common presentation among our antenatal patients in FMC Yenagoa. Lupus is variable in its presentation, course and outcome, and may sometimes mimic other medical conditions especially when it is not being looked out for, as was in this case.[6] The clinical manifestation may be confined to one organ system, with others becoming involved as the disease progresses. She presented with proteinuria even at booking (renal involvement), which is seen in about 50 percent of patients with SLE.[5] Common findings in SLE include anaemia, malaise, fever, arthralgia, myalgias, myopathy, rash, pleuropericarditis, photosensitivity and cognitive dysfunction.[7] Presence of certain antibodies can also cause endocarditis and valvular lesion which may lead to thromboembolic phenomenon.[8]

At booking, she had proteinuria which continued throughout pregnancy. This is an uncommon presentation in majority of pregnant women. It triggered a barrage of investigations in search for the cause, such as urinary tract infection, renal structural anomaly and chronic kidney disease.

More than 100 antigen-antibody pairs have been found in SLE[5]. Antinuclear antibody test, though not specific, has been described as the best screening test for SLE and it was markedly elevated in this patient.[5] Antibodies to double-stranded DNA and to Smith antigens which are relatively specific for lupus were normal and borderline respectively. Ds-DNA is present in about 62 – 72% of patient with SLE and anti-SM is presents in 30 – 38% of cases and it is specific for SLE.[5] She also had anaemia and thrombocytopaenia which are common features in patients with SLE.

Proteinuria and urine cast are found in half of patients with glomerular lesion and this may be associated with renal insufficiency. In SLE there may be elevated serum D-dimer level, which often follows a flare or infection. Although the diagnosis of SLE was made at delivery, she probably had a flare of the disease condition at 18-week gestation. Persistent elevation of D-dimer is associated with high risk of thrombosis in patients with SLE.[5]

The diagnosis of SLE in this patient was made using the revised criteria by the American rheumatism association for the diagnosis of SLE. It states that if 4 or more criteria are present at any time during the disease course, SLE can be diagnosed with 75 percent specificity and 95 percent sensitivity.[3,4,5] She had 9 out of the 11 criteria needed to make the diagnosis, these include malar rash, discoid rash, oral ulcers, arthritis, anaemia, leukopaenia, thrombocytopaenia, DVT, renal dysfunction, neurological disorder, and markedly elevated ANA. Also, her baby had features of lupus infant.

Over the past several decades, pregnancy outcomes in women with SLE have improved tremendously.[4,5] This is however influenced by active disease at the onset of pregnancy, age, parity, co-morbidity, obstetric complications and presence of antiphospholipid antibodies.[4,5] Lupus improves in a third of women during pregnancy, remains unchanged in a third and worsens in a third.[4,5] She had a flare during pregnancy. Pregnancy outcome is better if the disease has been quiescent for at least 6 months before conception, if there is no active renal involvement, absence of superimposed preeclampsia and no evidence of antiphospholipid antibodies activities.[5]

Management of SLE during pregnancy basically consists of monitoring the maternal clinical and laboratory conditions including foetal well-being. Monitoring of lupus activity during pregnancy and identification of pending lupus flares by a variety of laboratory technique have been recommended.[3,4,5] A number of numerical scales to emphasize ongoing disease activity have been advocated by some authors.[3-5] Components are weighed for severity with the SLE-pregnancy disease activity index and the lupus activity index. Serum complement levels are normally increased in pregnancy. Low levels of C_3, C_4 and CH_{50} are

associated with active disease while higher levels provide no assurance against disease activation.[5] This was however not done in this case, as there is no correlation between clinical manifestation of disease and complement levels.

Serial haematological studies were done for this patient, she had anaemia, leukocytopaenia and thrombocytopenia. These are indicators that may be seen in disease flare. Thrombocytopaenia may also indicate the onset of preeclampsia. Persistent proteinuria in patient with SLE in pregnancy has been described as an 'ominous' sign.[5] Careful attention was given to the development of hypertension, she had uterine artery Doppler scan at about 24 weeks which showed an increased resistivity index, thereby increasing the suspicion of early onset of preeclampsia.

Although SLE was diagnosed late in this case, the foetus was closely monitored for adverse effect. She had a dating scan, an anomaly scan and 4-weekly growth monitoring scans. In SLE complicated pregnancies, unless hypertension and its complications develop or there is evidence of foetal compromise or growth restriction, pregnancy is allowed to progress to term. Corticosteroids should be given and if she is a known SLE patient on steroid before conception, peripartum 'stress doses' of corticosteroids are given. High-dose glucocorticoid therapy is also recommended when severe disease supervenes (lupus flare). 'Pulse therapy' consisting of methylprednisolone 1 g given intravenously over 90 minutes daily for 3 days with a return to maintenance dose if necessary is also recommended.[5]

There is no cure for SLE and complete remission is rare.[3,4,5] NSAIDs have a role in its management, but their use is limited in pregnancy because of the risk of premature closure of the foetal ductus arteriosus.[5] Severe disease is managed with corticosteroids such as prednisolone, 1-2 mg/kg per day. After the disease is controlled, the dose is tapered to 10 – 15 mg daily, preferably each morning. In women who did not respond to conventional therapy, and those who develop serious complications, antibody-based immunoadsorption drugs can be used in pregnancy to remove autoantibodies and lipoproteins. Immunosuppressive agents like azathioprine 2 – 3 mg/kg daily is useful in controlling active disease and it has a good safety profile in pregnancy. Cyclophosphamide is another agent that can be used but it is teratogenic. It is not usually recommended during pregnancy but in life threatening conditions could be used after 12 weeks. Methotrexate and mycophenolate mofetil are other immunosuppressive drugs used in the management of SLE but should be avoided during pregnancy. Hydroxychloroquine is an antimalarial that has been shown to be useful in control of skin disease during pregnancy in patient with SLE. Although it crosses the placenta, it has not been linked with congenital malformations.[5]

It is pertinent to state that there was difficulty in seizure control in this patient using $MgSO_4$. It has been shown that in SLE, autoantibodies are directed against N- methyl- D- aspartate neuroreceptors which may cause neurotoxicity both in the foetus and in the mother. This may account for the poor response of this patient to $MgSO_4$ as she repeatedly had seizures (status epilepticus).

At the end of puerperium, there was marked regression of the skin lesion, proteinuria stopped, leukopaenia, thrombocytopenia and anaemia also reversed back to normal.

Adverse perinatal outcomes are significantly increased in pregnancies complicated by lupus.[4,5] Foetal complications include foetal growth restriction, preterm delivery, stillbirths and neonatal lupus. This baby had foetal growth restriction, neonatal lupus and there was neonatal death. Outcomes are worse with a lupus flare aswas the case. One of the reasons for adverse foetal outcome includes decidual vasculopathy with placental infarction and decreased perfusion. Anti-SS-A (Ro) and anti-SS-B (La) antibodies are also produced which may damage the foetal heart and conduction system, resulting in neonatal death.[4,5] This may perhaps be responsible for the death of this baby at home on the 28th day of life during her sleep giving that she was already diagnosed with heart block at birth.

CONCLUSION

Like a black cat in a dark night, SLE in pregnancy, a rare medical condition which we seldom encounter in our busy clinics could be missed especially in unsuspecting patients. Persistent proteinuria with skin rash should therefore raise a high index of suspicion, which should trigger a search for this life-threatening disease in pregnancy. Instituting the right management early in pregnancy with a multi-disciplinary approach will improve both maternal and foetal outcome and subsequently reduce maternal and perinatal morbidity and mortality.

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