New-onset systemic lupus erythematosus during pregnancy: a medical challenge

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ABSTRACT

Systemic lupus erythematosus (SLE) is a chronic autoimmune systemic disease which preferentially affects women in their reproductive years. SLE during pregnancy is associated with both maternal and fetal-neonatal complications. While most cases of SLE are diagnosed before conception, new-onset SLE during pregnancy or in the postpartum period is rare. This paper reports the case of a young nulliparous African patient, who had non-specific symptoms as from week 16 of gestational age. SLE was diagnosed at week 28 of pregnancy along with a life-threatening multisystem flare. This case illustrates how SLE can be difficult to recognize during pregnancy because the manifestations of the SLE may mimic normal physiological changes of pregnancy.

KEYWORDS

Systemic lupus erythematosus, SLE, pregnancy, autoimmune disease.

Introduction

Systemic lupus erythematosus (SLE) is a chronic autoimmune systemic disease which preferentially affects women in their reproductive years [1-6]. Every organ may be affected by SLE, including the kidneys, heart, lungs, blood, joints and skin. SLE is characterized by periods of flares and remissions [2]. Its incidence is approximately 0.3 – 23.7 per 100,000 person-years [3].

It is widely accepted that pregnancy during SLE is associated with a higher risk of maternal, fetal and neonatal complications [1-4,3].

In this paper, we report the case of a young nulliparous African patient who presented a first SLE flare during pregnancy. The diagnosis was delayed because the symptoms mimicked the physiological changes of pregnancy. SLE was finally diagnosed when a life-threatening multisystem flare occurred at week 28 of gestational age.

Case presentation

A 23-year-old African patient, primigravida, was complaining of fatigue, nausea, myalgia and joint pain at week 16 of gestational age. She had no particular medical history. The history of the pregnancy was unremarkable up to that point. Her symptoms were initially considered to be common and related to the pregnancy.

She was admitted to the emergency room at week 26 of gestational age for exacerbation of symptoms, mainly fatigue. Her blood test showed anemia (hemoglobin: 9.8g/dL and RBC: 358 106/mm^3), leucopenia (WBC: 3570/mm^3), C-reactive protein: 23.9 mg/L, and normal urea and creatinine levels (14 and 0.57 mg/dl respectively). She was discharged after 48 hours of hospitalization. She was again admitted to the emergency room at week 28 of gestational age for worsened shortness of breath, nausea, vomiting, diffuse myalgia and arthritis. She also mentioned fever (38°C) episodes at home.

Despite raised respiratory and heart rates (around 30 breaths/min and 128 beats/min), the physical examination was unremarkable apart from the symptoms described previously, mainly shortness of breath. Body temperature, blood pressure (130/90 mm Hg), and oxygen saturation (92%) were normal. A blood test showed anemia (hemoglobin: 10 g/dL) and leucopenia (WBC: 3500/mm^3) associated with a moderate inflammatory syndrome (C-reactive protein: 27 mg/L). There was no evidence of urinary tract infection. Blood gases showed low pO_2 (36 mm Hg) and normal pCO_2 (32 mm Hg). An electrocardiogram showed sinus tachycardia (115/min) without other abnormalities. Echocardiography showed significant pericardial and pleural effusion. X-ray examination of the chest confirmed the massive pleural effusion. Pleural puncture extracted 600 cc of a slightly turbid yellow fluid containing rare WBC and RBC, and 46.0 g/L of total proteins. Microbiological analysis was negative.

After the pleural puncture, the patient's symptoms worsened. Oxygen saturation decreased and her health state deteriorated very fast. Supplemental oxygen was delivered via nasal cannula (2L) and the patient was transferred to the intensive

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care unit where oxygen supplementation by nasal cannula (up to 3L) was continued. After 24 hours, once stabilized, she was admitted to an internal medicine ward in order to establish a definitive diagnosis. A new pleural puncture (650 cc) was performed after echocardiography showed increased pericardial and pleural effusion. In the meantime, obstetricians ensured pregnancy monitoring.

Oral ulcerations that had been absent a few weeks earlier were then observed.

Complementary investigations including a large panel of autoantibodies (Table 1) strengthened the suggestion of an autoimmune disease diagnosis, likely SLE, given that the patient fulfilled at least 5 (oral ulcers, arthritis, serositis, ANA, and immunologic disorders) of the 11 diagnostic criteria for SLE of the American College of Rheumatology (ACR) (Table 2). The ACR requires that the patient fulfill at least 4 of the 11 criteria.

In addition, anti-cardiolipin antibodies pointed to an anti-phospholipid syndrome, concomitant with SLE.

Table 1 Antibodies and serology.

ANA (titer)	> 1/1280	CMV	+
Anti-dsDNA (<50 IU/ml)	> 300	Rubella	+
Anti-Sm	++	Toxoplasmosis	+
ANCA	-	EBV	-
Anti-SSA (Ro)	+++	Borrelia	-
Anti-SSB (La)	-	TPHA	-
Anti-nucleosome	+++	HIV	-
Anti ribosomal P-protein	+++	Hepatitis B	-
Anti-Ku	-	Hepatitis C	-
Anti-U1RNP	-	Influenza	-
Anti-cardiolipin (< 18 U-GPL/min)	85		
Anti ß2GPI	-		
Lupus anticoagulant	-		

Table 2 ACR criteria for systemic lupus erythematosus.

Criterion	Definition
Malar rash	Fixed erythema, flat or raised, over the malar eminence, tending to spare the nasolabial folds
Photosensitivity	Skin rash as a result of unusual reaction to sunlight, by patient history or clinician observation
Discoid rash	Erythematosus raised patches with adherent keratotic scaling and follicular plugging, atrophic scarring may occur in older lesions
Oral ulcers	Oral or nasopharyngeal ulceration, usually painless, observed by a clinician
Arthritis	Nonerosive arthritis involving two or more peripheral joints, characterized by tenderness, swelling, or effusion
Serositis	Pleuritis (convincing history of pleuritic pain or rub heard by a clinician or evidence of pleural effusion) OR Pericarditis (documented by EKG, rub, or evidence of pericardial effusion)
Renal disorder	Persistent proteinuria greater than 0.5 g/day or greater than 3+ if quantitation not performed OR Cellular casts (may be red cell, hemoglobin, granular, tubular, or mixed)
Neurologic disorder	Seizures OR Psychosis (in the absence of offending drugs or known metabolic derangements)
Hematologic disorder	Hemolytic anemia (with reticulocytosis) OR Leukopenia - Less than 4000/mm^3 total on two or more occasions OR Lymphopenia - Less than 1500/mm^3 on two or more occasions OR Thrombocytopenia - Less than 100,000/mm^3 in the absence of offending drugs
ANA	An abnormal titer of antinuclear antibody by immunofluorescence or an equivalent assay at any point in time and in the absence of drugs known to be associated with "drug-induced lupus" syndrome
Immunologic disorder	Anti-DNA - Antibody to native DNA in abnormal titer OR Anti-Sm - Presence of antibody to Sm nuclear antigen OR Positive antiphospholipid antibody: 1. An abnormal serum level of IgG or IgM anticardiolipin antibodies, or 2. A positive test result for lupus anticoagulant using a standard method, or 3. A false-positive test result for at least six months confirmed by Treponema pallidum immobilization or fluorescent treponemal antibody absorption test

A treatment including low molecular weight heparin, aspirin and corticoid (methylprednisolone 60 mg per day) was introduced.

Thereafter, progressive kidney failure was observed along with moderate proteinuria (0.72 g/24 hours), suggesting an underlying lupus nephritis. On the obstetric side, monitoring of the growth of the fetus showed moderate intrauterine growth restriction, which was probably related to SLE-associated vascular insufficiency. Nevertheless, daily cardiotocographic monitoring was satisfactory.

After a period of clinical stabilization, the patient underwent a brief episode of psychotic disorder. The crisis was controlled with intramuscular injection of haloperidol and benzodiazepine medication. Cerebral MRI was normal.

The patient relapsed a few days later. Given the severity of the maternal condition and the need to administer treatments potentially toxic to the fetus, it was decided to proceed with delivery. A female fetus weighing 1470 grams (5th percentile) was delivered by cesarean section at week 31 and 4 days of gestational age. The neonate's Apgar score was 4/6/6. The medical condition of the baby quickly improved without any neonatal complications.

The medical condition of the mother also improved with an immunosuppressor treatment (methylprednisolone 1mg/kg and hydroxychloroquine 400 mg/day in association with azathioprine 2-3 mg/kg/day), which was adapted.

Discussion

This paper reports the case of a young nulliparous African patient, who had a first SLE flare during pregnancy. Serositis (pleuropericarditis) was discovered first, followed by lupus nephritis, and finally lupic psychosis. Given the severity of the mother's mental condition, we had no choice but to deliver the baby. Such disorders are already described, as about 50% of patients with SLE have neurological symptoms during the course of their disease [7,8] and 19 neuropsychiatric syndromes, including psychosis, have been associated with SLE. In addition, our patient presented a high risk, as it is noteworthy that corticotherapy may also be associated with psychotic disorders ("steroid-induced psychosis") [7], and she presented a high level of anti-ribosomal P antibodies, which have been associated with increased lupus psychosis (risk 5 to 30 times higher) [7].

While no early miscarriage is known to have been induced by SLE, in later pregnancy, SLE is associated with both maternal (lupus flares, worsening of renal function, preeclampsia, thrombotic events, hypertension) and fetal-neonatal complications (miscarriage, preterm birth, intrauterine growth retardation and neonatal lupus syndrome) [1-3,6,9,10]. This may be explained by increased hormone levels during pregnancy, especially of estrogens, which are known to be a risk factor for SLE development [6] .Elevation of prolactin and T-helper 2 cytokines also seems to be also involved [2]. Nevertheless, it is not clear whether or not disease onset is triggered by pregnancy [2,7].

In US SLE occurs in 13555 of 16.7 million pregnancies [6]. Most of these cases are diagnosed before conception. As it occurs in 0 to 13.5% of pregnancies with SLE, new-onset of SLE during pregnancy and in the post-partum period is a rare condition. Patients with first SLE onset during pregnancy usually present a more severe condition with a higher prevalence of renal and platelet involvement [4,9]. As in the aforementioned case, the onset of the disease tends to occur during the first and second trimesters (75% of patients) [2]. The outcome is better if SLE onset occurs during the third trimester of pregnancy [11].

Considering SLE-associated fetal outcomes, neonatal lupus (NL) is a syndrome characterized by different clinical features including cutaneous, hematological and hepatic manifestations, and a severe condition named complete heart block, which can lead to neonatal death [4,12,13]. NL is associated with maternal anti-SSA/Ro and anti-SSB/La antibodies, which are actively transported across the placenta from weeks 16 to 30 of gestation [1,4,10,13]. This background fully justified a cardiac fetal screening. Fortunately, our patient's baby was born without cardiac problems. That said, caution is required in the long term, as children born to mothers with SLE have a 3% increased risk of developing SLE during their lifetime [1]. In addition, the risks of congenital heart defects, learning disorders (dyslexia), autism spectrum disorders, attention deficit, and speech problems are also higher among these children [1,9].

Anti-phospholipid and anti-cardiolipin antibodies, as well as lupus nephritis, are also risk factors for adverse outcomes following pregnancy [9].

The main purpose of this paper is to highlight how difficult it can be to diagnose SLE during pregnancy. Indeed, the features of SLE may mimic normal physiological changes associated with pregnancy (e.g. thrombocytopenia, anemia, mildly elevated inflammatory markers, fatigue, arthralgia, myalgia, headaches, facial and palmar erythema, hair loss, mild resting dyspnea, mild edema) [1,2,5,12,13]. The diagnosis can be even more difficult to reach as some of the ACR diagnostic criteria for SLE can be observed during a normal pregnancy. The clinical symptoms and biological features of pregnancy and SLE are compared in Table 3.

Table 3 Comparison between pregnancy changes and SLE.

	Physiological pregnancy changes	SLE
Clinical symptoms	Fatigue Arthralgia Myalgia Headaches Facial and palmar erythema Hair loss Mild resting dyspnea Mild edema	Fatigue Arthralgia and arthritis Myalgia Headaches Facial and palmar erythema Fever without infection Lymphadenopathy Oral and nasal ulcerations Serositis Weight change Psychosis & delirium Peripheral neuropathies Vasculitis Splenomegaly
Biological features	Anemia Thrombocytopenia Mildly elevated inflammatory markers Proteinuria (< 300 mg per day)	Anemia Thrombocytopenia Leukopenia Lymphopenia Proteinuria

Likewise, distinguishing preeclampsia (PE) from lupus nephritis is also challenging due to overlapping features between the two conditions (e.g. proteinuria, renal impairment, hypertension and reduced platelet counts) [1,12,13]. Lupus nephritis and severe thrombocytopenia are more common in new-onset SLE occurring in pregnant compared with non-pregnant patients [4]. In addition to the risk of renal flare, pregnancy-associated renal hemodynamic changes may accelerate the decline of renal function and worsen hypertension and proteinuria [2, 10]. The medical management of the two conditions differs [1, 4]. Preeclampsie is a major concern in pregnant women with SLE as it affects 16 to 30% of SLE pregnancies compared with 5 to 7% of pregnancies in healthy women [13]. The timing of onset may help to distinguish lupus nephritis from PE, as PE usually occurs during the third trimester whereas lupus nephritis usually occurs during the two first trimesters [7]. However, the final diagnosis of lupus nephritis is based on renal biopsies, even though the risk of complications due to this procedure is high [2,3,10,13].

Conclusion

This paper illustrates how easily the diagnosis of SLE during pregnancy can be missed, given that features of SLE can mimic normal physiological changes occurring during pregnancy [1, 2]. Pregnancy is associated with several physiological changes that affect many major organ systems. Understanding these physiological adaptations to pregnancy is crucial for clinicians, as they have important implications for the diagnosis and management of various disorders, including SLE [14]. New-onset SLE during pregnancy and in the postpartum period is a rare condition which deserves to be highlighted as it may be associated with worrying maternal, fetal and neonatal complications [1,6,8].

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