Lupus-Induced Vasculitis and Multiple Organ Dysfunction Syndrome as the First Presentation of Systemic Lupus Erythematosus (SLE) in Pregnancy

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Patient: Female, 21-year-old
Final Diagnosis: Diffuse alveolar hemorrhage
Symptoms: Cough • dyspnea • fever • rash • sore throat
Medication: —
Clinical Procedure: —
Specialty: Rheumatology

Objective: Rare disease
Background: Systemic lupus erythematosus (SLE) is an autoimmune disease characterized by autoantibody production leading to inflammation in multiple organs; it commonly affects young women in their child-bearing years. Clinical manifestations are diverse and range from mild arthritis to diffuse alveolar hemorrhage (DAH). DAH is a rare and devastating complication of SLE that carries a mortality rate of up to 50%, despite aggressive therapy.

Case Report: A 21-year-old primigravida at 16 weeks gestation presents with a productive cough, rash, sore throat, and high-grade fever. Chest x-ray suggested multifocal pneumonia. Patient deteriorated despite antibiotics and intravenous (IV) fluids. She developed worsening anemia, leukopenia, and thrombocytopenia. Autoimmune work-up was positive for Coombs, antinuclear antibody, anti-smith antibody, and hypocomplementemia. Skin biopsy was consistent with SLE. SLE vasculitis was suspected. She required mechanical intubation for rapid respiratory deterioration, with CT thorax suggesting ARDS. Bronchoscopy was done and confirmed DAH. Her course was further complicated with retinopathy and acute pancreatitis associated with SLE. She was treated with IV steroids, IV cyclophosphamide, and plasmapheresis, with significant clinical improvement and successful extubation. She delivered a healthy baby at 32 weeks gestation.

Conclusions: Early recognition and initiation of treatment is critical to survival in DAH and requires a high index of clinical suspicion. Treatment includes high-dose steroids, cyclophosphamide, and plasma exchange. Pregnancy increases the risk of adverse outcome in SLE. Seven cases of DAH in pregnant patients with SLE have been reported. Here, we report a catastrophic presentation of DAH, acute pancreatitis, and retinopathy in a pregnant patient with newly diagnosed SLE.

MeSH Keywords: Hemorrhage • Lupus Erythematosus, Systemic • Pregnancy

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Background

Systemic lupus erythematosus (SLE) is an autoimmune disease that can affect virtually any organ in the body. It is most common in African-American and Hispanic women of child-bearing age. Untreated SLE in pregnancy has been related to more adverse outcomes [1,2]. In addition, uncontrolled SLE in pregnancy can be associated with exacerbations requiring immunosuppressive therapy [3], due to hormonal changes involving estradiol, progesterone, and prolactin, leading to a pro-inflammatory state [2]. There is also a higher morbidity and mortality in SLE patients with lower socioeconomic status. Non-white patients have a higher incidence of SLE, worse outcomes, and lower survival rates [2]. Previous epidemiologic studies have shown that African Americans are especially susceptible. Other ethnicities (e.g., Hispanics) are now being recognized as being at higher risk in the United States [2]. Diffuse alveolar hemorrhage (DAH) is a life-threatening complication of SLE and presents with hypoxemia, dyspnea, and a cough with blood-tinged expectoration. Mortality is high at 50%. The most common histopathological diagnosis is pulmonary capillaritis [4]. DAH as a manifestation of lupus is only seen in 1–5% of cases [4]. There have been only 7 cases reported of DAH in pregnancy. We report a case of a young, primigravida female at 16 weeks gestation who presented with cough, rash, sore throat, fever, chills, and dyspnea. CT thorax suggested bilateral pleural effusions with a differential diagnosis of DAH. She was also found to have acute pancreatitis and retinopathy associated with SLE during her hospitalization. SLE-associated acute pancreatitis and retinopathy are seen in 0.7–4% and 3–29%, respectively [5,6]. Retinopathy lead to serious visual deficits in up to 29% of patients with active disease [6]. A PubMed search using the keywords “DAH,” “SLE,” “acute pancreatitis,” “retinopathy,” and “pregnancy,” dating from 1990–2019 was performed.

Case Report

A 21-year-old previously healthy primigravida at 16 weeks of gestation with a past medical history of asthma, depression, and anxiety presented to an outside hospital (OSH), and had initially presented at an urgent care clinic for suspected streptococcal pharyngitis. There were no reported sick contacts and she was discharged on oral Amoxicillin 500 mg 2 times daily for 10 days, which she completed, but with no improvement. Two weeks after going to the urgent care clinic, she presented to the emergency department (ED) with fever and sore throat and was discharged home in stable condition. One week later, she broke out in a rash over her hands, feet, and mouth and was referred to our facility for escalation of care and bronchoscopy to rule out atypical infection. The patient remained febrile, tachycardic, and borderline hypotensive with systolic blood pressures in the 90–100s mmHg on days 3 and 4. She was started on high-flow nasal cannula for hypoxia. Her antibiotic regimen included intravenous (IV) azithromycin 500 mg daily (7 days total), IV cefepime (2 g every 8 h for 8 days), and IV vancomycin (750 every 8 h for 2 days, increased to 1250 mg every 8 h for 2 days). She was also treated with oral acyclovir 800 mg 5 times daily for 1 day, which was switched to IV acyclovir at 5 mg/kg (230 mg) every 8 h for 1 day. She had persistent fevers with tachycardia and tachypnea on days 2 to 4. She became acutely dyspneic and hypoxic to 88% oxygen saturation on room air on day 4 of admission, with repeat CXR suggesting bilateral pleural effusions with a differential diagnosis of multifocal pneumonia or pulmonary edema (Figure 1). The patient was suspected to have a complicated pneumonia and was treated with antibiotics (see above) and IV fluids. Despite management in the intensive care unit (ICU), her symptoms persisted. CT chest with contrast (Figures 2–4) showed bilateral airspace disease due to multifocal pneumonia versus infectious/inflammatory etiology.

Antibiotics were continued, but an extensive infectious workup was negative. Further infectious workup included negative Toxoplasmosis gondii PCR and Borrelia burgdorferi IgG/IgM antibody. Acid-fast bacilli cultures were negative. HIV antigen/antibody combo (fourth-generation) was negative. Her respiratory status deteriorated, requiring emergent endotracheal intubation and mechanical ventilation on day 4 of admission.
Her hemoglobin decreased from 7.9 g/dL to 5.7 g/dL on day 4 of admission, with worsening leukopenia 2.6 K/dL, thrombocytopenia 119 000 K/dL, and lymphopenia. Her peripheral smear was negative for signs of hemolysis. The patient had an immunological workup summarized in Table 1. The patient had a positive Coombs test, lactate dehydrogenase (LDH) that ranged from 415 to 789 IU/L (elevated), and haptoglobin at 109 (normal). Antinuclear antibody (ANA) was positive 1: 640 speckled pattern, anti-RNP 113, anti-Smith 103, complement C3 (26), and complement C4 (<8). Negative autoimmune serologies include anti-double-stranded DNA, anti-SSA/Ro, anti-SSB/La, and antiphospholipid antibodies. A skin biopsy was taken from the patient's lesions and showed interface dermatitis, vacuolar with atrophic epidermis, consistent with cutaneous lupus. There were also subtle foci of vascular damage, which raised the possibility of superimposed leukocytoclastic vasculitis. Bronchoalveolar lavage (BAL) confirmed suspicion of alveolar hemorrhage. BAL respiratory culture with gram stain grew 3000 colony-forming unit per mL of *Candida albicans*, which was also seen on fungal culture. Respiratory viral and bacterial panel were negative and included adenovirus PCR, coronavirus (KKU1, NL63, 229B, OC43) PCR, metapneumovirus PCR, rhinovirus/enterovirus PCR, influenza A (A/H1, A/H3, A/H1-2009) PCR, influenza B PCR, parainfluenza virus 1-4 PCR, RSV PCR, *Chlamydophila pneumoniae* PCR, and *Mycoplasma pneumoniae* PCR. Serum herpes simplex types 1 and 2 was not detected.
Table 1. Autoimmune workup.

| Autoimmune workup                  | Results                |
|------------------------------------|------------------------|
| Coombs test                         | Positive               |
| Antinuclear antibodies              | Positive               |
| Antinuclear antibody pattern        | 1: 640                 |
| Antinuclear antibody tilters        | Speckled               |
| Anti-deoxyribonucleic acid antibody (IU/mL) | Negative        |
| Anti-SSA                            | Negative               |
| Anti-SSB                            | Negative               |
| Serum C3 complement (mg/dL)         | 26                     |
| Serum C4 complement (mg/dL)         | <8                     |
| Anti-smith antibody                 | 10^7                   |
| Lupus anticoagulant                 | Negative               |
| Anti-cardiolipin antibody           | Negative               |
| Anti-beta-2-glycoprotein            | Negative               |

Parvovirus IgM was negative, and IgG was elevated at 0.97 (index). Tuberculosis QuantIFERON gold was negative. Tracheal aspirate acid-fast bacilli were negative times 4. Her estimated proteinuria was 1.83 g/24 h. Her urine sediment did not show dysmorphic cells or red blood cell casts, therefore, due to low suspicion for lupus nephritis, the patient did not have a kidney biopsy. Treatment was initiated with IV methylprednisolone 1 g for 5 days and plasmapheresis for 6 treatments, and she was continued on IV methylprednisolone 1 mg/kg.

Due to patient’s grave clinical status, a multi-specialty collaboration was performed, with shared decision-making with Rheumatology, Maternal Fetal Medicine, Transfusion Medicine, and Critical Care specialists. Due to the patient being intubated, a discussion with the patient’s mother to keep her pregnancy viable and initiation of treatment with cyclophosphamide was consented to after risks and benefits were reviewed.

Prior to treatment with her first dose of cyclophosphamide, the patient developed high fever, hypotension, and tachycardia on high-dose methylprednisolone. Blood cultures showed candidemia, which was treated with intravenous IV fluconazole. Ophthalmology evaluation was negative for viritis, but suggestive of bilateral cotton wool spots favoring retinopathy secondary to SLE. The patient was extubated and received cyclophosphamide IV 500 mg for initial dose, and 1 month later she received 840 mg (500 mg/m^2) on the day of discharge. On day 9 of admission, her course was further complicated with acute abdominal pain with lipase 1688, amylase 560, alkaline phosphatase 55 IU/L, total protein 5.2 g/dL, total bilirubin 1.0 md/dL, and albumin 2.6 g/dL. CT chest, abdomen, pelvis without IV contrast was performed to rule out mesenteric ischemia and peritonitis, and confirmed suspicion of acute pancreatitis. The patient was treated with cyclophosphamide prior to developing acute pancreatitis. Rheumatology and General Surgery believed the cause of acute pancreatitis to be due to high disease activity of SLE versus cyclophosphamide. However, drug-induced pancreatitis with cyclophosphamide was considered. The patient was discharged on hydroxychloroquine 200 mg twice daily and a prednisone taper with initial dose of 70 mg daily for 2 weeks, 60 mg daily for 1 month, 50 mg daily for 2 weeks, and 40 mg for 2 weeks prior to delivery. Of note, C-reactive protein level was not assessed during hospitalization due to initial presumed infection. The level was assessed at 1-month follow-up, and was <0.5 mg/dL (negative).

At 32 weeks gestation, the patient was found to have preterm premature rupture of membranes, which led to spontaneous labor. She was given magnesium sulfate for neuroprotection. She was also continued on outpatient oral prednisone 40 mg daily. The patient successfully delivered a healthy baby at 32 weeks gestation by vaginal delivery.

Discussion

SLE is an autoimmune disorder that primarily affects women of child-bearing age. Severe complications of SLE can include lupus nephritis and DAH. Acute pancreatitis is a rare manifestation of SLE, and other causes should be ruled out prior to making the association. SLE during pregnancy is more likely to cause a flare in an untreated primigravida woman. DAH is a rare and rapidly fatal association with SLE. The estimated mortality rate is 50%. However, recent case series have reported an 80% survival rate. DAH consists of 1.3–3.7% of hospital admissions associated with SLE. It usually presents in patients with a previous history of SLE. It can also present as the initial manifestation of lupus, although this is rare. The most common association with DAH is lupus nephritis, seen in about 70% of cases [7–9].

The differential diagnosis for DAH is broad and can be rheumatologic, infectious, coagulopathic, and pharmacologic. Rheumatologic causes include SLE, Goodpasture’s syndrome, antiphospholipid syndrome, and vasculitis. In pregnant women who present with hemoptysis, other causes need to be excluded prior to making the diagnosis of DAH [10]. This includes trauma, infection (tuberculosis, bacterial, viral, and fungal), malignancy (bronchogenic carcinoma, choriocarcinoma, or carcinoid), vascular (pulmonary hypertension, arteriovenous malformation, pulmonary embolism), connective tissue diseases (SLE, granulomatosis with polyangiitis, Goodpasture’s...
syndrome), cardiac (cardiomyopathy, mitral valve stenosis, congenital heart disease), pharmacologic (cocaine, anticoagulants, antiplatelets), and pseudoemphysema (gastrointestinal bleed or epistaxis) [10]. DAH can be a sepsis-mimicker. However, pregnant patient with SLE are susceptible to pneumonia. This is due to both immune dysregulation form SLE and immunosuppressive therapy [3]. In patients with no hemoptysis, diagnosis of DAH can be difficult, as in our case. [10] DAH presents with hypoxemia, dyspnea, and cough that can be blood-tinged. Hemoptysis can be seen in 44% of cases. Patients can also have fever or chest pain. DAH can be confused with pneumonia or pulmonary edema, as seen in our patient, who was initially treated with antibiotics at an OSH, but due to lack of clinical improvement she was transferred to a tertiary care facility. A CXR typically shows bilateral opacification with no peripher al involvement. CT thorax typically shows ground-glass opacifications. BAL shows increase in the number of hemorrhagic aliquots and hemosiderin macrophages that stain Prussian blue [11]. Biopsy shows diffuse alveolar damage, pulmonary capillaritis, and bland pulmonary hemorrhage [7].

There is a higher risk of complications in untreated and newly diagnosed patients with SLE during pregnancy [1,3]. However, it is not clear if parity has a higher risk of complications, as the data are controversial [3]. These complications can include preterm labor, pre-eclampsia, emergent C-section, deep vein thrombosis (DVT), infection, intrauterine growth restriction, intrauterine fetal death, and spontaneous miscarriage. There is also a 20-fold higher risk of maternal death [1]. Our patient was found to have preterm labor, likely related to SLE. There should be a multidisciplinary approach in the management of women of child-bearing age with SLE, and they should have a preconception risk assessment and pregnancy management with Maternal Fetal Medicine and Rheumatology. It is recommended that SLE should be controlled at least 6–12 months prior to conception. Managing SLE in pregnancy can be difficult, especially with no previous diagnosis, as seen in our patient. Our patient had a strong family history of SLE in her mother and grandmother, both suffering from their initial manifestation of SLE during their first and only pregnancy, stressing the importance of screening these patients prior to pregnancy [1].

There are no universal guidelines on management of DAH, including pregnant patients. This is due to lack of reported cases and clinical trials. Treatment is based on expert opinion, results of case series, and data from studies involving DAH associated with other types of vasculitis. High clinical consideration, early initial diagnosis, and aggressive treatment with pulse methylprednisolone in combination with cyclophosphamide are the mainstays of treatment for DAH. It is important to have a discussion with the patient about the ter atogenic effects of cyclophosphamide, as this drug can cross the placenta and is also associated with premature ovarian failure [1]. The risk of ovarian failure depends on the cumulative effect of the drug dose and the age of the patient, with older women having a higher risk due to less ovarian reserve [3]. The fetal effects of cyclophosphamide from in utero exposure remain unknown. Cyclophosphamide is currently pregnancy category X [3]. A study on the fetal effects of cyclophosphamide in mice was published in 2014 and showed a 6-fold increase of testicular cancer compared to the control group [12]. In addition, decreased spermatogenesis and ovarian follicle numbers were observed in the intervention group [12]. Rituximab has also been used successfully in several case reports, but is not considered the standard of care. Supportive treatment with mechanical ventilation and blood transfusions should be considered if necessary. Plasmapheresis, which helps removes antigen-antibody complexes from the blood, may be used for refractory cases [1,5]. Whether plasmapheresis improves survival is unknown [1].

There are only 7 case reports of DAH in pregnancy. Table 2 summarizes each case with the year the case was published, age of gestation, treatment modality, and outcome of the pregnancy. In 4 of the 7 reported cases of DAH complicating SLE in pregnancy, the decision was made to terminate the pregnancy and then administer cyclophosphamide. One patient received azathio-prine initially, but with recurrence of DAH, IV cyclophosphamide was used. All 7 patients survived. Patients ages ranged from 23 to 38 years old, and gestation age ranged from 17 weeks to 35 weeks. Patients were diagnosed with SLE 13 years, 10 years, 6 years, and 1 month (2 cases) prior to their presentation of DAH. Two cases were diagnosed with SLE in the antepartum period. The first case involved a 38-year-old at 28 weeks gestation requiring emergent C-section due to fetal bradycardia. She was found to have DAH with hemoptysis seen on endotracheal tube during C-section, with radiologic findings and BAL confirming DAH. She was subsequently diagnosed with SLE with positive immunologic findings, lupus nephritis, antiphospholipid syndrome, lymphocytopenia, and thrombocytopenia [10,13–15].

In the second case, a 35-year-old patient at 30 weeks gestation was diagnosed with DAH. She was initially diagnosed with SLE at 21 weeks gestation. She was suspected to have DAH at 30 weeks gestation when she presented with dyspnea and hemoptysis. Non-contrast CT thorax showed diffuse ground-glass opacities and nodular consolidation. She was treated with pulse methylprednisolone, with some improvement. She delivered a healthy baby at 31 weeks gestation. After C-section, she had a BAL, which confirmed DAH and she was treated with cyclophosphamide and pulse steroids. Her respiratory status had deteriorated, despite these treatments. She was treated with extracorporeal membrane oxygenation and plasmapheresis a total of 3 times, with successful extubation and improvement in respiratory status. Pregnancy was terminated in 4 out of 6 cases [16].
These cases raise the question of whether immediate delivery in a viable pregnancy should be done when DAH is diagnosed. There are no current guidelines on delivery of the baby in a pregnant patient with DAH. In addition, the prognosis of DAH with delivery is unknown. In cases of high disease activity from SLE refractory to treatment, delivery should be considered [16]. Further studies are needed to determine treatment guidelines and timing of delivery in pregnant patients with SLE and DAH [16]. Current recommendations include a multidisciplinary approach with multiple specialties and expert opinion, in conjunction with having a thorough discussion with the patient, weighing the risks (e.g., fetal growth restriction and SLE aggravation) and benefits of maternal and fetal outcomes [1,16].

Furthermore, our patient was found to have acute pancreatitis likely associated with SLE. Acute pancreatitis is rare in SLE, seen in only 0.7–4% of cases [5]. It is important to rule out pharmacologic, obstructive, and toxic causes of acute pancreatitis before attributing it to SLE. Etiologies of pancreatitis in lupus can be due to medications used to treat lupus, like azathioprine, cyclosporine, and, rarely, cyclophosphamide [5]. Cyclophosphamide was given prior to our patient developing acute pancreatitis and was a considered etiology. However, the patient’s high disease burden of SLE was believed to be the primary cause of acute pancreatitis. There is 1 reported case of DAH and acute pancreatitis in a young non-pregnant female treated successfully with rituximab and cyclophosphamide [5].

We presented a catastrophic case of lupus-induced vasculitis with multiple organ dysfunction syndrome with manifestations of retinopathy, DAH, and acute pancreatitis, with a prevalence of less than 5% for each. This patient had unusual serologic results, with no detectable plasma anti-dsDNA antibodies and a high titer of anti-Smith antibodies. It has been universally accepted that anti-dsDNA antibodies are correlated with disease activity in SLE patients, especially with lupus nephritis. However, a recent study demonstrated that anti-dsDNA is correlated with clinical and serologic criteria, with no effect on disease activity [17]. In our patient, it is unclear if these manifestations developed as the initial presentation of SLE or if these complications developed as a result of delayed diagnosis and treatment of SLE.

| Author                  | Year | Age, yrs | GA, wks | Diagnosis, yrs | SLE manifestations | MV | Termination | Treatment        | Outcome (mother) |
|-------------------------|------|----------|---------|----------------|-------------------|----|-------------|------------------|------------------|
| Blitz and Fleischer     | 2018 | 23       | 17 (prima) | 17             | Heme, lupus nephritis, skin | No | Yes         | MP, CYC, PLEX    | Survived         |
| Ng et. al. [10]         | 2017 | 38       | 32      | 38             | Skin, nephritis, hematologic, APS | Yes | No          | Prednisone       | Survived         |
| Gaither et al. [13]     | 2005 | 22       | 23      | 12             | Nephritis        | No | No          | MP, CYC          | Survived         |
| Keane et al. [14]       | 1997 | 23       | 21      | 12             | Skin, arthritis  | Yes| Yes         | MP, AZA, CYC, PLEX| Survived         |
| Chang et al. [15]       | 2002 | 26       | 29      | 26             | DAH, nephritis, arthritis | Yes | No          | PO CYC, MP, PLEX, CVVH | Survived, Successful Delivery |
| Chang et al. [15]       | 2002 | 35       | 22      | 35             | DAH, APS         | Yes| Yes         | MP, PLEX, CVVH, CYC | Survived         |
| Kim et al. [16]         | 2019 | 35       | 30      | 35             | Nephritis        | No | No          | MP, CYC, PLEX    | Survived         |

Prima – primigravida; MV – mechanical ventilation; APS – antiphospholipid syndrome; CYC – cyclophosphamide; FLEX – plasmapheresis; PO – by mouth; AZA – azathioprine; CVVH – continuous veno-venous hemofiltration; DAH – diffuse alveolar hemorrhage; wks – weeks; yrs – years; MP – methylprednisolone; SLE – systemic lupus erythematosus; GA – gestational age.
Conclusions

DAH is a life-threatening disease that has a high mortality rate. Early recognition and prompt treatment are important for survival. Undiagnosed and untreated pregnant patients with SLE are more likely to have complications in pregnancy, especially when diagnosis is delayed, and close monitoring is crucial. This case demonstrated a catastrophic presentation of SLE in a pregnant patient with severe multiple organ dysfunction syndrome involving the pulmonary, hematologic, dermatological, ocular, and gastrointestinal systems. In our case, the patient’s lack of response to antibiotics for sepsis, strong family history of SLE, and diagnostic workup prompted our team to pursue the alternative diagnosis of SLE. The patient’s respiratory failure, decrease in hemoglobin, and chest x-ray with worsening opacities heightened our suspicion of DAH. Our case highlights the importance of using a multi-specialty approach for management of this rapidly fatal condition. After using a collaborative approach, treatment with steroids, plasmapheresis, and cyclophosphamide led to survival of both mother and fetus. Further guidelines are needed for management of pregnant patients with SLE and DAH and timing of delivery.

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Conflict of interest

None.

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