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Case Report

Systemic lupus during pregnancy with refractory alveolar haemorrhage: recovery following termination of pregnancy

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A case of refractory pulmonary hemorrhage in a pregnant 22-year-old with systemic lupus is presented. The clinical difficulty of management of pulmonary haemorrhage and lupus flare during pregnancy are discussed.

Keywords: pregnancy; pulmonary haemorrhage, lupus flare

Case report

A 22-year-old female was diagnosed with SLE having presented with arthralgia, oral ulcers and a malar rash. She had a history of Raynaud's disease since the age of 12 years. ANA was positive at 1:640, anti-DNA antibodies were positive at 286 Iu/ml, ESR was 16. She was commenced on hydroxychloroquine with improvement of her rash but not her joint pain.

She was admitted 14 months later complaining of dyspnoea and pleuritic chest pain. She had no haemoptysis. Chest radiographs (CXR) revealed diffuse alveolar infiltrates. Laboratory investigations showed haemoglobin of 9.4 g/dl, pH 7.44, pO_2 50 mmHg, pO_2 25 mmHg, saturation 86% on room air. Pulmonary function obtained on admission showed FEV_1 2.73 (87% predicted), FVC 3.00 (83% predicted), DLCO was 145% predicted. She was noted to have 3+ proteinuria and was 21 weeks pregnant. Bronchoscopy revealed grossly blood stained lavage and many haemosiderin laden macrophages. No infectious pathogens were found despite an aggressive search. A diagnosis of diffuse alveolar haemorrhage was made and pulse methylprednisone was started (500 mg daily for 3 days). She improved with this treatment and azothioprine was added 4 days later.

Six days later she had recurrence of her symptoms with a fall in her haemoglobin to 6.9 g/dl. She was transferred to the University of Michigan where a blood gas revealed pH 7.47, pO_2 67 mmHg, pCO_2 30 mmHg, saturation 92% on 100% face mask. She was intubated and placed on mechanical ventilation. CXR revealed diffuse infiltrates (Figure 1). The 24-h urine collection revealed 2.7 g protein. BUN was 18 mg/dl with a serum creatinine 0.3 mg/dl. The ANA was positive 1:2560, and antibodies to double-stranded DNA were minimally elevated by the Farr assay at 11 (range 0–7). The patient did not have IgG or IgM anticardiolipin antibodies, and had negative tests for antibodies to RNP, Sm, Ro and La. The VDRL was negative and the partial thromboplastin time was 20.6 (normal 22.8–29.1 s). Because of the life threatening nature of her illness, she was commenced on once pulse of cyclophosphamide 0.5 g/m^2 and methylprednisilone 1 g every day for 3 days. Plasmapheresis was also started 4 L/day for 4 days. Over the next few days she improved and was extubated after 9 days of mechanical ventilation. She continued to improve, with associated radiographic clearing (Figure 2), until 8 days later when she became confused with features of acute psychosis. Magnetic resonance imaging of the brain did not show any evidence of lupus cerebritis and spinal tap revealed normal CSF. A presumptive diagnosis of steroid psychosis was made and her prednisone was reduced to 30 mg daily.

Eight days later her pulmonary haemorrhage recurred with diffuse infiltrates on CXR (Figure 3) and a fall in haemoglobin to 7.3 g/dl. Platelets at that time were 89 000/mm.^{3} She was again intubated. Two days later her platelet count had fallen to 45 000/mm^3 and her bilirubin was increased at 2.6 mg/dl, hemoglobin was stable at 9.0 g/dl. At the time of admission the clinical presentation was not suggestive of pre-

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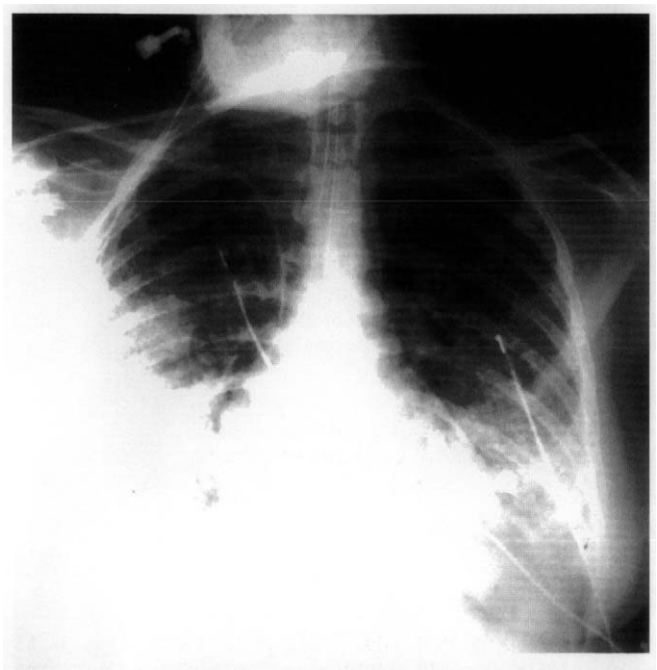

Figure 1 Chest radiograph following intubation showing diffuse infiltrates.

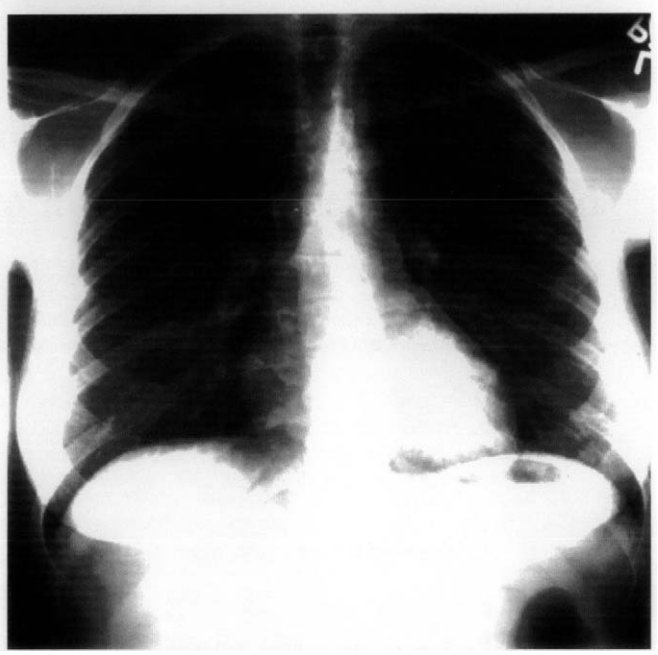

Figure 2 Chest radiograph after extubation demonstrates radio graphic improvement.

eclampsia based on normal blood pressure and platelet count. Ultrasound at that time revealed a single viable fetus at 20 weeks gestation by biometric parameters and normal amniotic fluid volume. Due to the recurrence of her pulmonary haemorrhage a repeat ultrasound was performed. Biometric measurements suggested less than a week's growth over the 3 weeks since admission. In addition oligohydramnios was noted. Although the clinical parameters of both lupus exacerbation and superimposed pre-eclampsia overlap so much, the diagnosis of superimposed pre-eclampsia was considered. The lack of fetal growth and the development of oligohydramnios were felt to be incompatible with fetal survival. Therefore termination of pregnancy was offered and performed using Misoprostol. Three days later her platelet count was 163 000/mm^3 and her pulmonary status had improved (Figure 4). The following day she was extubated after 10 days of mechanical ventilation. Oral cyclophosphamide was commenced. Over the next 2 days her CXR returned to normal (Figure 5).

She continued to improve and was discharged from hospital 7 weeks after her initial presentation on oral cyclophosphamide and prednisone.

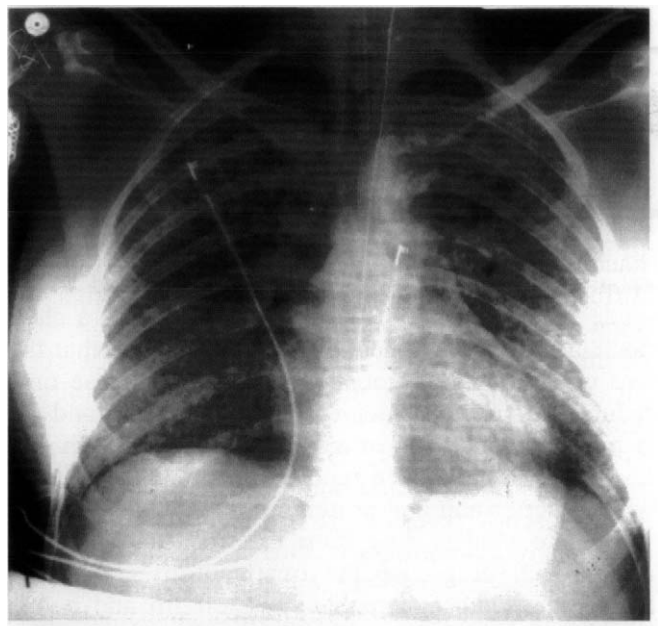

Figure 3 Chest radiograph following recurrence of pulmonary haemorrhage showing recurrence of diffuse infiltrates.

Discussion

Pulmonary haemorrhage is a rare but potentially catastrophic complication of SLE. Earlier studies reported a mortality of 50–90%[1] although a recent study[2] reported a 75% survival. Clinical features are nonspecific, but diffuse alveolar infiltrates, hypoxemia, dyspnoea and anaemia are characteristic.

Lupus pregnancy is, by definition, high risk because of the increased fetal loss[3] and incidence of preterm delivery.[4–7] The incidence of maternal lupus flares during pregnancy is controversial and appears to

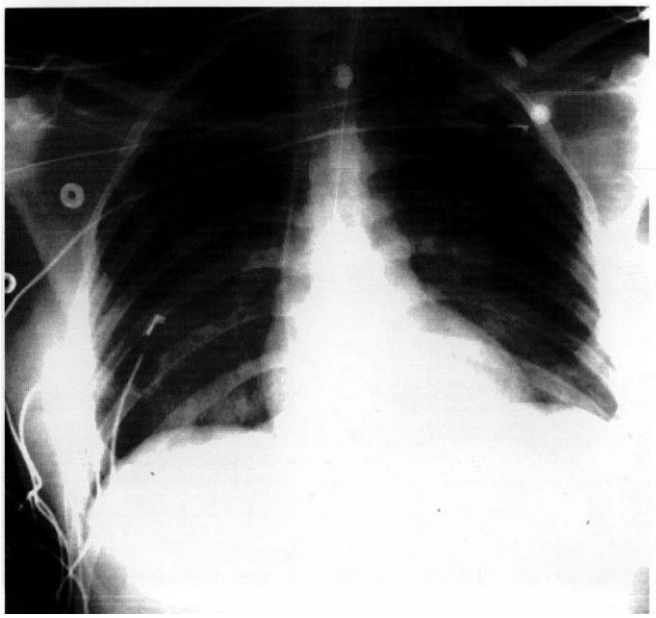

Figure 4 Chest radiograph three days following termination of pregnancy showing radiographic improvement.

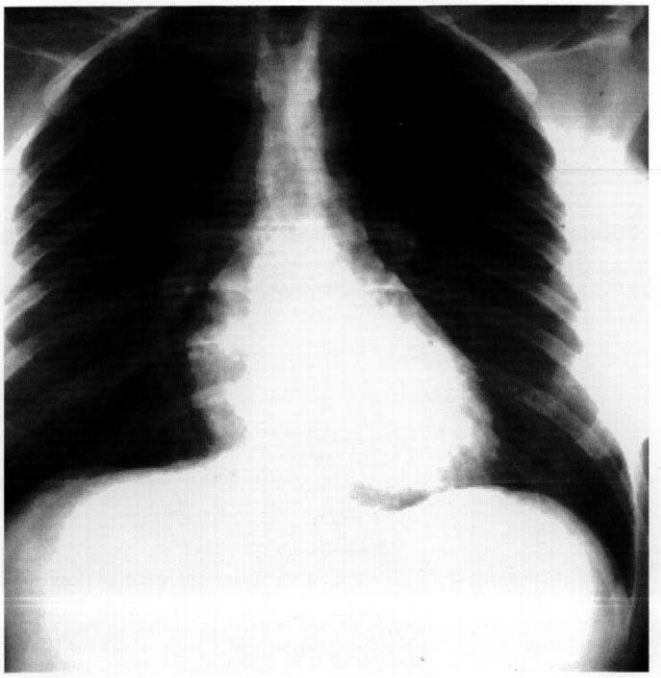

Figure 5 Chest radiograph 5 days following termination of pregnancy showing return to normal.

be related to the severity of disease, socioeconomic status and the predominance of immune complex disease.[8,9] Flares in the postpartum period are well recognized.[9,10] There is an increased risk of pre-eclampsia, pregnancy induced hypertension and the syndrome of hemolysis, elevated liver enzymes, low platelets (HELLP) in lupus pregnancy.[11,12] It can be difficult to differentiate between a lupus flare and pre-eclampsia and this differentiation may need to be made in 25% of pregnancies.[9] In many cases a clear distinction cannot be made and it is possible that the two conditions may coexist.[11] Lack of increase or a reduction in the complement components C3 and C4 is more characteristic of a lupus flare[13] although low levels of C4 have been reported in pregnant patients with hypertension and proteinuria.[14]

Low to modest dose corticosteroids and possibly antimalarial drugs are the treatment of choice for active lupus during pregnancy. Cleft lip and palate have been described as side-effects of corticosteroids in animals; however, these have not been reported in humans.[15] Growth retardation has been reported at higher doses. Azothioprine has been used extensively in pregnancy in women with renal transplants with no increase in birth defects[16] although this has not been confirmed in all studies.[17] Cyclophosphamide is clearly teratogenic in animals[18] and a malformation rate of 22% has been described in humans.[15] Consequently cyclophosphamide is used in pregnant women with SLE only when life threatening immune complex disease is refractory to other therapies.

Due to the rarity of alveolar haemorrhage complicating lupus, prospective, controlled trials evaluating therapy have not been performed. The treatment of choice is high dose steroids with or without cyclophosphamide; plasmapheresis has been used with anecdotal reports of success.[1] In randomized controlled trials plasmapheresis plus prednisone and cyclophosphamide were no more effective than prednisone and cyclophosphamide alone for severe lupus nephritis.[19] Consideration of plasmapheresis should be reserved for patients with severe alveolar haemorrhage refractory to corticosteroids and cytotoxic agents.

Our patient presents many of the dilemmas discussed above. She developed a lupus flare during the second trimester manifested as pulmonary haemorrhage, she had proteinuria without hypertension or an active urinary sediment. Her alveolar haemorrhage was refractory to treatment with steroids and azothioprine necessitating the use of cyclophosphamide, with its associated risks, in association with plasmapheresis. There was initial improvement with this treatment; however, pulmonary haemorrhage recurred despite the treatment with cyclophosphamide and plasmapheresis. She subsequently developed an elevated bilirubin and low platelets which along with her refractory pulmonary alveolar haemorrhage resolved after delivery of the fetus.

This case demonstrates the clinical difficulty of managing a lupus flare in pregnancy. In addition the

clinical parameters used to make the diagnosis of superimposed pre-eclampsia and HELLP syndrome may not be specific enough to differentiate between the two disease entities and may reflect a similar pathophysiological pathway.

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