

# Pulmonary involvement in neonatal lupus: a challenging diagnosis – case report and literature review

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## ABSTRACT

**Introduction:** Pulmonary involvement is relatively frequent in adult and juvenile patients with Systemic Lupus Erythematosus (SLE), but its occurrence in newborns with Neonatal Lupus Erythematosus (NLE) is exceedingly rare.

**Case report:** A mother with SLE and positive anti-SSA/Ro and anti-SSB/La delivered a preterm newborn with third-degree heart block and positive anti-SSA/Ro confirmed postnatally. A temporary pacemaker was placed at D3 and a definitive pacemaker only at D15 due to sepsis with concurrent mild respiratory failure. Despite adequate antibiotic therapy, negative cultures and decreasing inflammatory parameters, at D17 severe respiratory failure ensued, requiring mechanical ventilation. Chest x-ray showed symmetrical interstitial infiltrates. Acute Lupus Pneumonitis (ALP) and Pulmonary Embolism were suspected and the chest angio-CT revealed diffuse ground glass opacities. After 3 methylprednisolone pulses he improved rapidly.

**Discussion:** The diagnosis of ALP in NLE, mostly one of exclusion, is a challenge. A high degree of suspicion and a multidisciplinary approach to these patients are fundamental in order not to delay establishing a diagnosis. Although few reports in the literature, early aggressive treatments are probably crucial for a favorable outcome without long-term sequelae.

**Keywords:** Anti-SSA/Ro antibodies; Interstitial Lung Disease; Neonatal Lupus Erythematosus

## INTRODUCTION

Neonatal lupus erythematosus (NLE) is a distinct clinical entity<sup>1</sup>. It is a very rare disease related to the transplacental passage of maternal autoantibodies and characteristic illness in the fetus/neonate<sup>1-7</sup>. In approximately 95% of cases, mothers have autoantibodies against SSA/Ro, SSB/La or, rarely, anti-U1RNP. However, 50% of affected infants have healthy mothers and maternal seropositivity often is discovered after an affected infant is born<sup>1,4,5,8</sup>. The other half of infants are born to mothers who have diagnosed rheumatic conditions, such as Systemic Lupus Erythematosus (SLE)<sup>4</sup>. NLE infants rarely have undetectable SSA/Ro antibodies, but in those instances they usually have other autoantibodies, SSB/La and U1RNP<sup>2,5</sup>. It is considered a model of passively acquired autoimmunity<sup>1</sup>. Environmental factors and fetal genetic components may contribute to the pathogenesis of NLE or amplify the effects of the antibodies, which may be necessary but insufficient in causing the tissue injury<sup>1</sup>.

NLE includes several clinical manifestations: congenital heart block (CHB) and cutaneous lupus are the most common, while hepatobiliary disease, hematological manifestations and central nervous system involvement may occur<sup>1,2,4,6</sup>.

Pulmonary involvement is relatively frequent as pleural effusions/pleuritis and less frequently as pneumonitis or alveolar hemorrhage in SLE cases, but its occurrence in newborns is exceedingly rare<sup>6</sup>. To our knowledge there have been only few reports of NLE-related pneumonitis. In these cases, the pneumonitis was transient and some of the reports occurred in the setting of cardiac disease. The authors present a case of

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Acute Lupus Pneumonitis (ALP) in a newborn with NLE, its diagnosis, treatment and course.

## CASE REPORT

We report the case of a newborn delivered from a mother with SLE and positive anti-SSA/Ro and anti-SSB/La with a previous child with NLE who died at two years-old due to complications from myocarditis. There was no further family history of autoimmune or pulmonary disease.

A prenatal diagnosis of heart block was established at 20 weeks (ventricular heart rate [HR] 50-55 bpm), despite maternal treatment with hydroxychloroquine and prednisolone during pregnancy and salbutamol and dexamethasone after the diagnosis. The newborn was delivered by elective caesarean section at 36 weeks, with an Apgar score of 9/10 (1<sup>st</sup> and 5<sup>th</sup> minutes) and was electively admitted to Neonatal Intensive Care Unit (NICU). A rough erythematous rash on the trunk and back was observed at birth but resolved spontaneously in 48 hours. The standard electrocardiography revealed complete atrioventricular block with auricular sinus rhythm, HR 140 bpm and junctional ventricular rhythm with HR 55-60 bpm. Anti-SSA/Ro were confirmed. The echocardiogram showed a structurally normal heart, enlargement of cardiac chambers and dilated left ventricle (end-diastolic diameter 21 mm, end-systolic diameter 10.8 mm) and preserved global ventricular systolic function; patent ductus arteriosus (PDA).

A temporary pacemaker was placed at D3 and a definitive pacemaker only at D15 due to suspected sepsis: at D8 there was thrombocytopenia (60,000/mm<sup>3</sup>), leucopenia (4,180/mm<sup>3</sup>) and an elevation of C Reactive Protein (CRP) from 17.3 to 90.4 mg/L. He received a course of intravenous vancomycin, gentamicin and cefotaxime. Chest radiograph was normal.

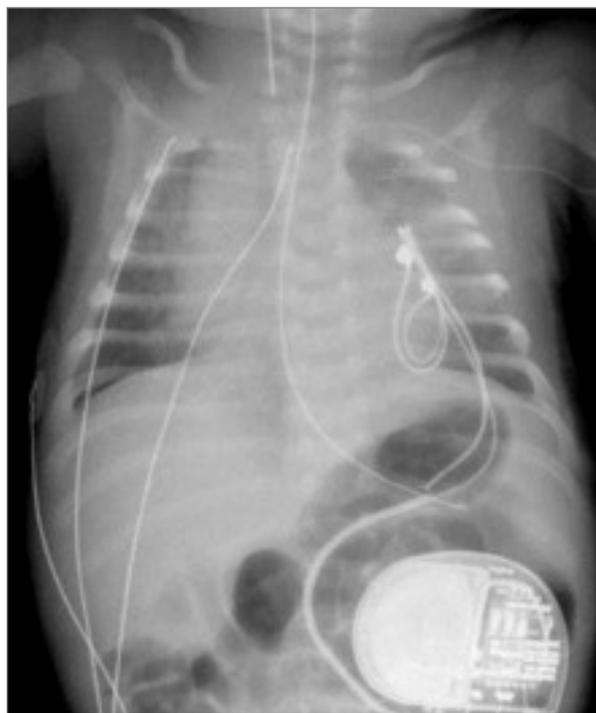
At D12, due to clinical and laboratory worsening (maximum CRP 178.4 mg/L), meropenem was added with a favorable response. Blood and temporary pacemaker transducer's cultures identified *Staphylococcus epidermidis*. Urine and Cerebrospinal Fluid (CSF) cultures were negative. He received a definitive pacemaker at D15, without apparent complications.

Despite ongoing antibiotic therapy, negative cultures and decreasing inflammatory parameters, at D17 severe Acute Respiratory Failure (ARF) ensued, requiring Mechanical Ventilation (MV) (maximum FiO<sub>2</sub>

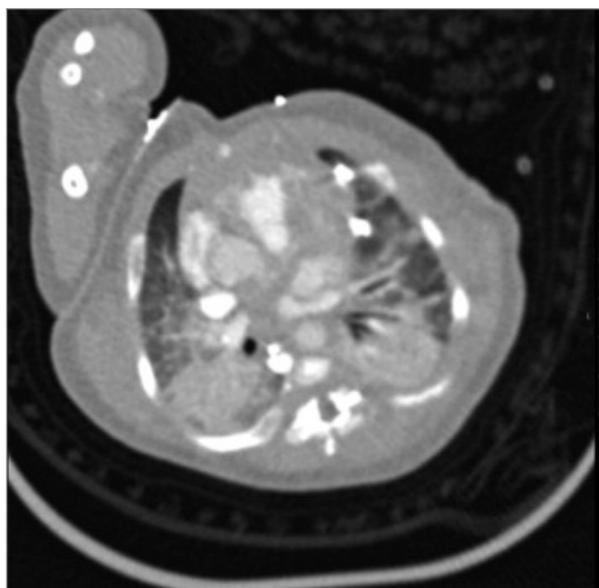
0.4). On examination, the newborn was afebrile but tachypneic and hypoxemic. Auscultation revealed diffuse rhonchi and crackles. His skin showed no rashes or petechiae, there was no arthritis and neurologic examination, as well as the remainder of his physical examination, was normal.

The white blood cell count was 19,670/mm<sup>3</sup>, with 6450/mm<sup>3</sup> polymorphonuclear neutrophils, 160/mm<sup>3</sup> band forms, and 9230/mm<sup>3</sup> lymphocytes. Hemoglobin and hematocrit were 8.9 g/dL and 26.8%, respectively, and the platelet count was 187,000/mm<sup>3</sup>. He received two Red Cell Concentrates Transfusions (RCCT) on D17 and D23. Maximum serum total bilirubin was 4.95 mg/dL. Transaminase enzymes, electrolytes, renal function, urinalysis, coagulation studies remained normal. CRP increased to 87.3 mg/L, ESR was 24 mm/1<sup>st</sup>h. Cultures remained negative and no viral agents were identified. Chest ultrasound excluded pleural effusions. Echocardiogram and electrocardiogram showed mild leakage through a Patent Foramen Ovale (PFO) and normal pacemaker function.

Serial chest radiographs showed progressively worsening with symmetrical diffuse interstitial infiltrates (Figure 1). D-dimer elevation (19,73 mg/ml) was



**FIGURE 1.** Chest radiograph: symmetrical diffuse interstitial infiltrates



**FIGURE 2.** Computed Tomography Angiography: diffuse ground glass opacities with consolidations in posterior sections of parenchymal lung

observed. ALP and Pulmonary Embolism were suspected and Computed Tomography (CT) Angiography revealed diffuse ground glass opacities with consolidations in posterior sections of parenchymal lung (Figure 2); a thrombosis of the infrarenal inferior vena cava was incidentally found but Pulmonary Embolism was excluded. Assuming the exclusion of other possible causes for this ARF, a diagnosis of ALP was presumed. At D24, the patient received three intravenous methylprednisolone pulses (30 mg/kg/day), followed by oral prednisolone (1 mg/kg/day), and improved markedly. Lung infiltrates disappeared, MV was stopped 48 hours after the methylprednisolone pulses and supplemental oxygen weaned within 6 days.

He was discharged home on D46, asymptomatic, receiving enoxaparin and weaning prednisolone, with normal ventricular function and no pulmonary hypertension on echocardiogram. A cranial ultrasound was performed on D32, which was normal.

His immunological studies showed positivity for Anti-Nuclear Antibodies (ANA-1/320 speckled pattern), anti-SSA/Ro (>240 units) and anti-dsDNA (142.7 UI/mL), negativity for anti-SSB/La, anti-RNP, antiphospholipidic and lupus anticoagulant antibodies and no decrease in complement levels.

At 3-months-old, following a viral bronchiolitis, he developed a *Haemophilus influenzae* pneumonia with ARF requiring MV for 14 days and antibiotic treatment.

At 8 months of age, all antibodies became negative. Control pulmonary CT (20 months) revealed areas of subsegmental atelectasis in both lower lobes, likely sequelae of the respiratory infection. Currently, at 24 months, the patient shows no respiratory distress, normal auscultation findings, no hypoxia, and normal growth and psychomotor development. He maintains follow-up as an outpatient at Neonatal, Pediatric Pulmonology, Cardiology and Rheumatology clinics.

## DISCUSSION

In NLE, attention has been mostly focused on cardiac and cutaneous involvement, although multisystem organ involvement has also been described. Lung involvement is a rare manifestation of NLE and has presented as transient pneumonitis<sup>6</sup>. In this report we describe a newborn who had the classic CHB and hematologic findings of the NLE and developed ARF, which might be attributed to NLE-related pneumonitis.

NLE rashes tends to be photosensitive, but may be present at birth or in non-sun exposed areas. Skin lesions often appear as annular erythematous plaques<sup>5,7,8</sup>; less common skin findings include erosions, alopecia, vitiligo, cutis marmorata, telangiectasia congenita, and morphea-like changes<sup>2</sup>, none of which were present in our patient who presented with a transient rough erythematous rash. The characteristics, timing and rapid resolution without treatment supports that this was not a manifestation of NLE.

The most frequently described cardiac findings in NLE are conducting abnormalities. NLE accounts for 85% of all cases of congenital CHB<sup>2-4</sup>. It is thought that this arises from anti-Ro antibody-directed injury to cardiac conducting cells, resulting in fibrosis. Structural changes like PDA, ventricular and atrial septal defects, coarctation, mitral and tricuspid insufficiency, hypoplastic right ventricle and PFO have also been reported<sup>2</sup>. In our newborn, a PFO was found in addition to CHB.

Autoimmune hemolytic anemia, thrombocytopenia, and neutropenia are seen in a small proportion of affected infants<sup>1,2</sup>. Our patient did not have anemia at birth, but later developed anemia requiring RCCT. This might also be related in part to the concomitant infection during the time of physiologic anemia.

Hepatobiliary abnormalities including increased transaminase enzymes, which have been reported in approximately 9-25%, did not occur in our pa-

tient<sup>1,2,4,8</sup>. Hepatosplenomegaly is usually secondary to passive congestive changes from CHB-related heart failure<sup>2</sup>. Zuppa et al recommending clinical and laboratory monitoring since the highest incidence of hematological features and liver tests changes are observed at 3 months of age<sup>1</sup>.

Cerebral dysmaturation, ventriculomegaly and lenticulostriate vasculopathy are recently described manifestations<sup>4</sup>. Rhizomelic chondrodysplasia punctata, nephritis, and multiorgan failure are rare<sup>4,8</sup>. Coexisting antithyroid and antiphospholipid antibodies may complicate the presentation<sup>4</sup>. These findings were not observed in our patient.

Noncardiac NLE often has a mild, transient, and self-limited course requiring only sun protection. Nevertheless, long-term sequelae can cause significant morbidity, so infants benefit from comprehensive evaluation and early intervention<sup>4</sup>. Complete CHB causes significant morbidity and mortality, with more than 2/3 of surviving neonates ultimately requiring pacemakers, and a cumulative probability of death of 20% at 3 years<sup>1,4,5,7,8</sup>.

Pulmonary manifestations may be a life-threatening complication<sup>9,10</sup>. In a case series of ALP as presentation of SLE the mortality was 40%<sup>11</sup>. Treatment of ALP is based on case reports or small series and involves high dose steroids; other immunosuppressive drugs such as azathioprine, cyclophosphamide, and intravenous immunoglobulin may be used for severe cases refractory to corticosteroids<sup>9,11,12</sup>. In our patient, clinical and radiological signs markedly improved with intravenous methylprednisolone pulses; MV was required and weaning was obtained after corticosteroid therapy. Early diagnosis, close monitoring, and appropriate intervention with immunosuppressive treatment may subvert organ-threatening disease in selected cases<sup>4</sup>. ALP has been reported in infants with no apparent infection, however, a case of a *Pneumocystis carinii* infection was described. In this case the pneumonitis presented in a febrile child, making it questionable whether it was NLE-related or secondary to an infection<sup>2</sup>. In our case, no infectious agent was identified, and the marked response after starting corticosteroids supports that this pneumonitis was a manifestation of NLE, as opposed to an unidentified infection. ALP may resolve or progress to chronic interstitial pneumonitis<sup>10</sup>. There are no well-defined recommendations for lung biopsy indications in patients with ARF<sup>9</sup>, which was not performed in our newborn due to its invasive nature and a positive therapeutic response. The pathology find-

ings in ALP include interstitial pneumonitis, hyaline membranes, alveolar necrosis, edema, microvascular thrombosis and focal polymorphonuclear infiltration without evidence of vasculitis, but there are no pathognomonic histopathologic features<sup>9,10</sup>.

In mothers with SLE, the disease activity during pregnancy is a risk factor for neonatal morbidity, with 75% of affected infants being admitted to the NICU. The incidence of CHB recurrence rate in subsequent pregnancies is 15%-18% in infants born to mothers who have anti-SSA/Ro or anti-SSB/La antibodies<sup>4,7,8</sup>. Our newborn's mother has SLE with anti-Ro antibodies and had a previous child who died from NLE myocarditis. This context increased awareness for an early diagnosis of NLE in this case. However, pulmonary involvement was a diagnostic challenge, since excluding other causes in a newborn in an NICU with several co-morbidities poses an important diagnostic dilemma for the neonatologist and pediatric rheumatologist. Because infections are a leading cause of death in patients with lupus, all pulmonary infiltrates should be considered infectious until proven otherwise<sup>9-11</sup>.

The high frequency of anti-Ro antibodies in NLE and the observation that NLE-skin lesions spontaneously resolve as maternal autoantibodies are eliminated from the infant's circulation provides evidence that these antibodies might play a pathogenic role in this disorder and are regarded as an immunologic marker<sup>1,2,4</sup>. The factors determining whether infants develop CHB or skin disease are not yet known and there are controversies in the literature<sup>2,3</sup>. Antibodies against the 52/60-kD SSA/Ro and 48-kD SSB/La ribonucleoproteins are associated with CHB, whereas antibodies against the 50-kD SSB/La are associated with cutaneous disease. Anti-U1RNP autoantibodies are usually associated with atypical cutaneous lesions without cardiac or systemic abnormalities in a small number of NLE cases and may play a role in the pathogenesis of thrombocytopenia<sup>3,5,7,8</sup>. As more NLE case reports are described, it may become clearer whether a relationship exists between serologic subtypes and the clinical manifestations. Zuppa et al disclosed that anti-SSA/Ro antibodies persisted at 9 months of life in 10% of infants of their study, suggesting a timing for follow-up<sup>1</sup>.

Asymptomatic mothers and infants with NLE are at risk of developing autoimmune disease in their lifetime, particularly SLE and Sjogren syndrome in the mothers. Long-term observation of patients by pediatric rheumatology is therefore advised for complete

evaluation, monitoring, management, and long-term follow-up of affected infants<sup>3-5,8</sup>.

In conclusion, there are few reports of ALP in NLE and its diagnosis is a challenge as it is mostly one of exclusion. A high degree of suspicion by neonatologists and a multidisciplinary approach to these patients are fundamental in order not to delay establishing a diagnosis. Although very little has been reported in the literature, early aggressive treatment is probably crucial for a favorable outcome without long-term sequelae.

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